Using EEG to investigate premature aging and cognitive decline in adults with Down's Syndrome

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This dissertation is submitted for the degree of Doctor of Philosophy

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Declaration

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration except where specifically indicated in the text.

This dissertation is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University of similar institution except as declared in the Preface and specified in the text.

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Summary

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Thesis title: Using EEG to investigate premature aging and cognitive decline in adults with Down's Syndrome

Down's Syndrome (DS) is a genetic disorder associated with intellectual disability, accelerated aging and a propensity for early-onset Alzheimer's disease (AD). Beta-amyloid plaques are one of the pathological hallmarks of AD, and also a common characteristic of the older DS brain. AD treatment trials are now moving towards administration of the intervention at preclinical stages, with the goal of preventing cognitive decline in the first place, rather than trying to halt or reverse existing pathology. Consequently, it has become essential to develop biomarkers of AD, which can: 1. Predict clinical changes and 2. Track the effectiveness of putative preventative treatments. The strong association between DS and AD means that this research is particularly important for people with DS and it presents a high-risk group for exploring predictive biomarkers.

Electroencephalography (EEG) is a non-invasive and inexpensive measure of cortical activity, which is being evaluated with the typically developing (TD) population as a potential biomarker of AD. This thesis aims to evaluate EEG as a potential predictor of cognitive decline associated with DS-AD. There are several potential EEG measures that could be explored. Following a review of the literature, the predictive potential of the following event-related potentials (ERPs): mismatch negativity (MMN) and P300 (P3a and P3b), were chosen for exploration with cross-sectional and longitudinal investigations.

The thesis begins by exploring how the ERPs differ for a cross-section of 36 adults with DS and 39 age- and gender-matched TD controls. As expected, the MMN waveform was smaller for adults with DS than TD controls. However, the P3b waveform was predominantly absent for adults with DS, whilst the P3a response was significantly enlarged. The P3a response was also enlarged for the adults with DS who scored lower on a

neuropsychological measure. The neuropsychological measure indexes frontal functions, which are compromised early in DS-AD.

This experiment also provided evidence that MMN was related to age in DS, with increasing latencies and decreasing amplitudes for older participants. The differences in MMN amplitude between the groups (DS, TD) were isolated to the older adults. These findings lend support to the premature aging hypothesis of DS.

The thesis also included a longitudinal follow-up in which 34 adults with DS underwent a repeated cognitive examination one year after their EEG and initial cognitive assessment. The analyses found that adults with DS who had lower MMN amplitudes at the initial assessment were more likely to decline at the cognitive follow-up. This finding suggests that MMN may be a potentially useful clinical tool for predicting the cognitive decline associated with DS-AD.

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List of Abbreviations

11C–PIB	Selective carbon–11 labelled radioisotope Pittsburgh compound B
µV	Micro-volts
μV^2	Micro-volts-squared
β-amyloid	Beta-amyloid
Aβ	Beta-amyloid
ACE-R	Addenbrookes Cognitive Examination-Revised
ad	Inter-aural, auditory deviant
AD	Alzheimer’s disease
APP	Amyloid Precursor Protein
BACE-1	Beta-secretase 1
BADS-C	Behavioural Assessment of the Dysexecutive Syndrome
Ca^{2+}	Calcium
CAMCOG-DS	The Cambridge Cognitive Examination for Older Adults with Down's Syndrome
CAMDEX-DS	The Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities
CEFA	Cambridge Executive Functioning Assessment
CIDDRG	Cambridge Intellectual and Developmental Disabilities Research Group
Cl-	Chloride
CPFT	Cambridgeshire and Peterborough NHS Foundation Trust
CSF	Cerebral Spinal Fluid
dB	Decibels
DCM	Dynamic Causal Modelling
DS	Down’s Syndrome
DSA	Down’s Syndrome Association
DS-AD	Down’s Syndrome and Alzheimer’s disease
EEG	Electroencephalography
EF	Executive function
EFDS	Executive Function test battery for people with Down’s Syndrome
EGI	Electrical Geodesics
EMG	Electromyography
ERP	Event related potential
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FWHM	Full Width at Half Maximum
FWE	Family-wise error
gd	Global deviant
GFP	Global field power
GP	General practitioner
gs	Global standard
hAPP	Human amyloid precursor protein
Hz	Hertz
ICA	Independent Component Analysis
ID	Intellectual disability
IQ	Intelligence quotient
JDR	Join dementia research
KBIT-II	Kaufman Brief Intelligence Test, second edition
KOhms	Kilo Ohm
ld	Local deviant
ls	Local standard
MATLAB	Matrix laboratory

MCI	Mild cognitive impairment
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
ms	Milliseconds
MSE	Multi-scale entropy
Na+	Sodium
NAID	Neuropsychological Assessment of Dementia in Individuals with Intellectual Disability
NFT	Neurofibrillary tangles
NMDA	N-methyl-D-aspartate
NRES	National Research Ethics Service
PET	Positron emission tomography
PFC	Prefrontal cortex
PIB	Pittsburgh compound B
PIC	Patient identification centre
PPI	Pre-pulse inhibition
PSP	Post synaptic potential
qEEG	Quantitative electroencephalography
QFPCR	Quantitative Fluorescent Polymerase Chain Reaction
R&D	Research and Development
RFT	Random Field Theory
SIB	Severe Impairment Battery
SOD-1	Superoxide dismutase
SPM	Statistical Parametric Mapping
T1	Time 1 (cross-sectional assessment)
T2	Time 2 (longitudinal assessment)
T2-T1	Time 2 – time 1 (assessment difference)
TD	Typically developing
ToL	Tower of London
WBIC	Wolfson Brain Imaging Centre
WHO	World Health Organisation

1 Chapter 1. General introduction

1.1 Study purpose

One of the most striking observations in Down's Syndrome (DS) is the remarkably high rates of Alzheimer's disease (AD), which presents a significant burden beyond the associated intellectual disability (ID). We are beginning to consider the biochemistry behind AD and develop aligned treatments. However, the treatments will only be of use if we can determine who will benefit, in time to benefit. This thesis aims to explore an inexpensive and non-invasive technology called electroencephalography (EEG). The technology has been used previously with the general population to compare typically developing adults to those who have AD or DS. In light of the high risk, early onset and homogenous acquisition of AD in DS this thesis now aims to evaluate EEG as a predictor of the associated cognitive decline.

1.2 Chapter overview

The chapter begins by describing the DS brain, from synapses to cortical structure. Then the aetiology and pathology of AD are discussed, with a view to exploring the interaction between the two disorders (DS-AD). Synaptic dysfunction is a theme throughout the chapter because: 1. Synaptic function forms the basis of neurocognitive function, 2. Synaptic abnormalities are one of the earliest indicators of AD development, and 3. Widespread pathology at a synaptic level will likely generate abnormal EEG signals. This thesis is primarily concerned with evaluating the extent to which EEG can predict the associated features of AD (aging, cognitive decline). More specifically, the EEG products to be explored are event-related potentials (ERPs): mismatch negativity (MMN) and P300 (P3a, P3b). The introduction concludes by describing how: 1. Potential predictors (biomarkers) of DS-AD can be evaluated, and 2. The ERPs have been previously related to DS, typical and pathological (AD) aging. The overall aim of this thesis is to evaluate the ERPs (MMN, P3a, P3b) as potential predictors of the cognitive decline associated with DS-AD.

1.3 Down’s syndrome

1.3.1 Trisomy 21

John Langdon Down first described the phenotypic features of Down’s Syndrome (DS) 150 years ago (1866). The phenotypical features of DS include a flat nasal bridge and short stature (Roizen & Patterson, 2003). From a cognitive perspective, people with DS typically present with deficits in memory and language (Lott & Dierssen, 2010). Indeed, DS is the commonest identified cause of intellectual disability with a prevalence of 1 in every 650 to 1000 live births (Bittles, Bower, Hussain, & Glasson, 2007). DS is a genetic disorder attributed to the triplication of chromosome 21 (Lamb et al., 1996), which was first demonstrated by LeJeune et al. (1959). DS results from the full trisomy in 95% of cases, with Robertsonian translocations and mosaicism accounting for the remaining 5% (Hunter, 2010).

1.3.2 Head and brain morphometry

One of the marked phenotypic features of DS is the head morphology, which is brachycephalic (Roizen & Patterson, 2003). Furthermore, the DS profile, specifically the nasal bridge, is stereotypically flatter than that of TD controls (Roizen & Patterson, 2003). The DS brain is typically 20% smaller than typically developing (TD) population brains (Roizen & Patterson, 2003), and becomes comparatively smaller still for older adults (50+ years) (Mann, Royston, & Ravindra, 1990). Specific regions of the brain that are notably smaller in DS include the: cerebellum, brainstem and frontal lobes (Ross, Galaburda, & Kemper, 1984; Schmidt-Sidor, Wisniewski, Shepard, & Sersen, 1990). In contrast, the ventricles are disproportionately enlarged in DS (Pearlson et al., 1998); whilst the cerebral sulci have less depth and the gyri are less complex than is the case in TD individuals (Aylward et al., 1997; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001; Teipel et al., 2004; Teipel et al., 2003). The developmental, neural abnormalities in DS are further exacerbated by the brain atrophy of aging (Teipel & Hampel, 2006). This thesis is an EEG study of adults with DS, which acknowledges the atypical head and brain morphometry by: 1. Overcoming the flat profile, and maximising comfort, by elevating the facial adjustments of the EEG kit with a paper bridge at the nasal bridge; 2. Allowing for atypical electrode positions to be maximal for the event-related potentials (ERPs) of interest by employing an across-scalp, rather than single canonical electrode, approach to the analyses. This approach is detailed in chapter 2, section 2.13.

1.3.3 Neurons

The reduced brain size in DS is potentially explained by the reduced number of cortical neurons in this group (Larsen et al., 2008). A stereology study by Larsen et al. (2008) compared the brains of four DS foetuses with controls to show that, at 19 weeks of gestation, the DS foetuses had an average of 6.85 billion neocortical cells (neurons and microglia), which is a 34% reduction compared to controls. Indeed, a morphometry study of children with DS (birth – 12 years) found reduced neuronal density at between 20 and 50% (Wisniewski, Laure-Kamionowska, & Wisniewski, 1984). This reduction in neuronal density has been most consistently reported in the granular layers (Ross et al., 1984; Schmidt-Sidor et al., 1990). Although the DS brain is smaller and has fewer neurons than average, the radial columns are wider but less numerous. This is evident in the abnormal cortical stratification seen in DS foetuses (22 weeks) (Schmidt-Sidor et al., 1990). Furthermore, the columns are wider and more widely dispersed for children with DS than TD children (Buxhoeveden & Casanova, 2002).

1.3.4 Dendrites

Beyond arguments about neuronal density, dendritic structure and number are altered in the cortex and hippocampus in DS (for a review see Fiala, Spacek, and Harris (2002)). Dendrites are the primary receptive vehicle for neurons (Kasai, Matsuzaki, Noguchi, Yasumatsu, & Nakahara, 2003; Sorra & Harris, 2000). Furthermore, synapses are formed at dendritic spines (DeFelipe & Fariñas, 1992) therefore an abnormal dendritic structure would predict abnormal synaptic function (Belichenko et al., 2004). The nature of the dendritic abnormalities have been grouped in three types of spines: long, thin and irregularly distributed; short; or, very large and sparsely distributed (Marin-Padilla, 1976). Dendritic abnormalities are progressive throughout the life-course. Up to the age of 2.5 months, the dendritic branching in layer III pyramidal cells of the prefrontal cortex is comparable between DS and TD (Vukšić, Petanjek, Rašin, & Kostović, 2002). However, in DS, by the age of two years the dendritic branching and length (apical, basal) has been reported to fall below normal levels (Becker, Armstrong, & Chan, 1986). For older adults with DS (no AD), the number of dendritic spines in the pyramidal neurons (apical, basilar areas) is reduced further still (Suetsugu & Mehraein, 1980). Typically, the number of dendritic branches and spines increase between birth and 15 years, after which time the number gradually declines (Sachio Takashima, Ieshima, Nakamura, & Becker, 1989). However, in DS the dendritic increase during childhood is minimal whereas the decline during adulthood is maximal (Takashima, Lida, Mito, & Arima, 1994). Dendrites play a range of essential roles: from the functioning of synapses to connectivity in the whole brain (Diaz, Sanchez, Duchen, Nakano, & Perez, 2016; Kasai et al., 2003; Sorra & Harris, 2000). Therefore, the abnormal dendritic structure in DS could be mechanistic for the impaired cognitive functioning reported for this group (Contestabile, Benfenati, & Gasparini, 2010).

1.3.5 Synaptic and functional deficits

Cognitive functions such as learning and memory are underpinned by communication at a synaptic level (Benfenati, 2007). Therefore the cognitive impairment associated with DS may be the result of abnormal dendritric structure, and the inevitable compromise of synaptic function (Contestabile et al., 2010). Cognitive functions that are served by the hippocampus, such as learning and memory, are frequently impaired in DS (Pennington, Moon, Edgin, Stedron, & Nadel, 2003). DS mouse models have found that hippocampal dendritic spines are abnormal, which leads to altered synaptic function and plasticity (Contestabile et al., 2010). In Ts62Dn mice, slices have been tested from the hippocampal region: CA1, to find a reduction in long-term potentiation (LTP) due to induction failures (Siarey, Stoll, Rapoport, & Galdzicki, 1997; Siarey et al., 1999). The increased inhibition of N-methyl-d-aspartate (NMDA) receptors (NMDARs) has been postulated as the physiological basis for the induction failure because the administration of a $GABA_A$ receptor antagonist (picrotoxin) has been shown to restore LTP (Belichenko, Kleschevnikov, Salehi, Epstein, & Mobley, 2007; Costa & Grybko, 2005; Kleschevnikov et al., 2004). As demonstrated in DS-mouse models focused on the hippocampus, an imbalance between inhibitory and excitatory neurotransmission compromises synaptic plasticity (Belichenko et al., 2004; Keck, Hübener, & Bonhoeffer, 2017; Kleschevnikov et al., 2004).

The hippocampus uses synaptic plasticity to support memory function (Contestabile et al., 2010). Memory can be characterized as implicit or explicit. Implicit memory formation is an automatic process, which requires limited attentive effort (Graf & Schacter, 1985). In contrast, explicit memories are formed from an attentive and intentional learning process (Graf & Schacter, 1985). The relative strengths and deficits in DS memory processing demonstrate this dichotomy. In a study by Vicari, Bellucci, and Carlesimo (2000), 14 children with DS performed comparably to mental-age matched TD children on tasks which required implicit memory, but were significantly impaired on explicit memory tasks. In experimental environments, adults with DS have demonstrated insufficient attention (Krinsky-McHale, Devenny, Kittler, & Silverman, 2008), poor information coding and unsuccessful retrieval strategies (Carlesimo, Marotta, & Vicari, 1997), which inevitably leads to impaired explicit memory. For older adults with DS, the common association of memory deficits with the disorder poses a challenge for disentangling the intellectual disability from a dementia diagnosis.

1.3.6 Accelerated aging in Down’s Syndrome

In the literature, the terms ‘premature’ and ‘accelerated’ are used interchangeably to describe aging in DS (Oliver & Holland, 1986; Zigman, 2013). The average life expectancy of people with DS has significantly increased in recent years from 12 years old in the 1940s to an average of 57.8 years old for women and 61.1 years old for men, in developed countries (Bittles et al., 2007; Glasson et al., 2003). However, average life expectancy for adults with DS is still much lower than the general population in the UK (81.2 years) and USA (79.3 years) (WHO, 2016). This comparatively reduced life expectancy has leant support to the argument that aging is accelerated in DS. Indeed, accelerated aging in DS is evident across several physiological systems: from earlier menopause to premature skin wrinkling (see Zigman, 2013 for a review).

The calcification of the basal ganglia in DS, which can begin as early as 5 years old, has been postulated as a neurological indicator of accelerated aging in DS (Ieshima, Kisa, Yoshino, Takashima, & Takeshita, 1984; Mann, 1988). Furthermore, a machine learning exploration of structural MRI scans found that the average, predicted brain age for 46 adults with DS was 2.49 years older than 30 typically developing (TD) controls (Cole et al., 2017). However, predicted brain age was highly variable within the DS group because of individual differences in Aβ deposition and cognitive impairment (Cole et al., 2017). Indeed, accelerated aging to the neurological system is largely characterised by early-onset Alzheimer's disease (AD) in DS (Zigman, 2013).

Adults with DS not only develop AD at earlier ages than the general population, but at a much higher rate (Holland, Hon, Huppert, Stevens, & Watson, 1998). Indeed, by the age of 50 everybody with DS has the neuropathological hallmarks of AD: Aβ plaques(Mann, 2006), and almost half (40%) display clinical symptoms (Holland, Hon, Huppert, Stevens, & Watson, 1998). The strongest predictor of AD is chronological age. However, there is contention as to whether the risk for AD development is related to a specific "age" range, or is an inevitable part of the "aging" process if one were to live long enough (Ritchie & Kildea, 1995).

1.4 Alzheimer's disease

1.4.1 Introduction to Alzheimer's disease

Alois Alzheimer first described the pathological features of AD in 1907. The description was based on the post-mortem examination of a 51 year old woman who had exhibited memory loss and unusual behaviours in the later stages of her life (Alzheimer, Stelzmann, Norman Schnitzlein, & Reed Murtagh, 1995). The dysfunction and loss of synapses is a significant feature of AD (Selkoe, 2002). However, the disease pathology is typically characterised by severe cortical atrophy, neurofibrillary tangles (NFTs) containing hyperphosphorylated tau and beta-amyloid (Aβ) plaques (Korczyn, 2008). The first symptom of AD is typically anterograde memory decline, which is later followed by language impairment and executive dysfunction (Feldman & Woodward, 2005; Small et al., 1997). Beyond, the cognitive dysfunction associated with AD, a clinical diagnosis also includes a deficit in everyday skills (Richards et al., 1999).

1.4.2 The amyloid cascade hypothesis

The 'amyloid cascase hypothesis' proposes that the deposition of the insoluble, neurotoxic, Aβ protein is the primary determinant of AD (Hardy & Higgins, 1992). The hypothesis offers that excessive quantities of Aβ, either from over-production or ineffective clearance, leads to the formation of Aβ plaques, then neurofibrillary tangles (NFT) and neurodegneration (Hardy & Higgins, 1992; Hardy & Allsop, 1991; Hardy & Selkoe, 2002; Selkoe, 1991). Aβ results from the amyloidogenic cleavage of APP by β-secretase (BACE-1), and then γ-secretase (Selkoe, 1990). The cleavage process is displayed in figure 1.1, which includes the non-amyloidogenic pathway that produces harmless peptides. β–amyloid, the end product of the amyloidogeneic pathway, can aggregate into soluble monomers and dimers, which do not, in of themselves, pose a neurotoxic problem (Haass & Selkoe, 2007). Alternatively, insoluble fibrillar formations can occur which, in a sheet structure, results in β–amyloid deposits (De Strooper, Vassar, & Golde, 2010).

β–amyloid deposits are at the core of senile plaques – a hallmark of AD. In conclusion, this process of cleaving and aggregating β–amyloid is hypothesised to set off the pathological cascade towards clinical AD.

Of course, there is resistance to the amyloid cascade hypothesis, including a recent call from Herrup (2015) to reject the hypothesis all together. Herrup (2015) primarily discredits that there is a linear relationship between Aβ and dementia. Herrup (2015) goes on to promote alternative mechanisms of AD development, such as tauopathy, autophagy failure, neuroinflammation and mitochondrial dysfunction. A recent reflection on the amyloid cascade hypothesis, which is co-authored by one of the model's originators (Hardy), concurs that "a linear relationship between amyloid-β and dementia is not teneable" (Hardy & De Strooper, 2017, pg. 854). However, this is framed within the context that AD drug development should acknowledge the input and interactions between multiple mechanisms of AD development, rather than view the hypotheses competitively (Selkoe et al., 2016). This thesis acknowledges the other mechanisms of AD development but has only described the amyloid cascade hypothesis because of the strong genetic connection to DS-AD (section 1.5.2).

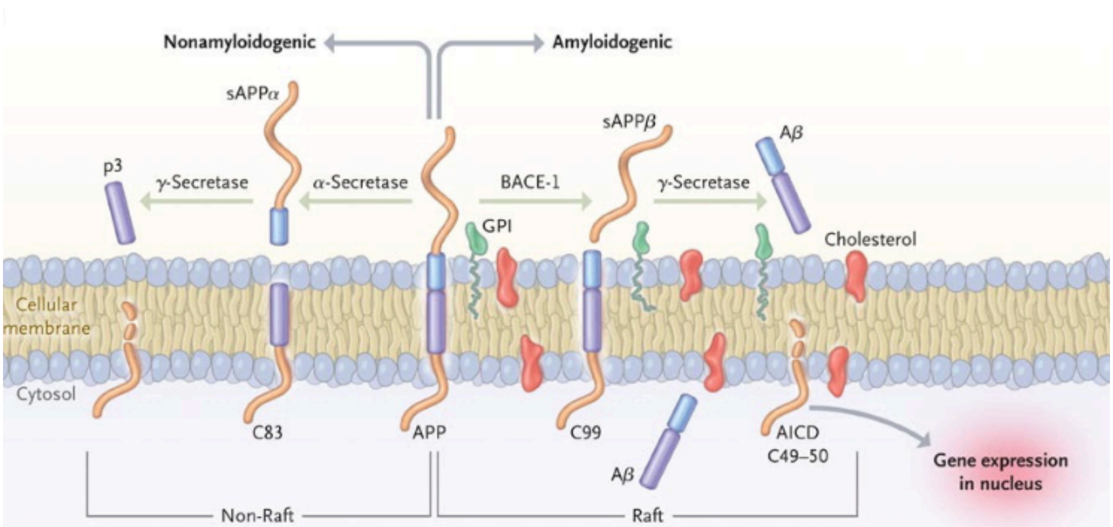

Figure 1.1. The intracellular processing of the amyloid precursor protein from Querfurth and LaFerla (2010).

1.5 *Alzheimer's disease in Down's Syndrome*

1.5.1 *High risk of AD in DS*

Adults with DS are at very high risk of developing the pathological features of AD. Indeed, Aβ deposits are seen in the brains of people with DS by the second or third decade of life (Mann, 1988) and Aβ plaques by the fifth decade of life (Mann, 2006). Furthermore, 40% of people with DS over the age of 50 are living with AD (Holland et al., 1998), which rises to 75% over the age of 60 (Ball et al., 2006). The proposed reason behind this risk is associated with the genetic aetiology of DS, as described below in section 1.5.2.

1.5.2 *The genetic basis of DS-AD*

DS is the caused by the triplication of chromosome 21 (Wiseman et al., 2015), where the APP gene is located. Therefore, due to a gene dosage effect, adults with DS have a life-long overproduction of the peptide product cleaved from APP: Aβ (Wiseman et al., 2015). Inline with the amyloid cascade hypothesis, this gene dosage effect is postulated to be the primary causative factor for high rates of AD in DS (Hardy & Higgins, 1992). Chromosome 21 also codes for the superoxide dismutase 1 (SOD1) gene (Zana, Janka, & Kálmán, 2007), which may explain why AD is not only more prevelant in DS, but has a much earlier onset (Cenini et al., 2012). SOD1 creates hydrogen peroxide product from superoxide (Sea et al., 2014), the overproduction of which causes oxidative stress (Levanon et al., 1985; Sinet, 1982). Oxidative stress is linked with aging, which supports an accelerated aging model of DS (Finkel & Holbrook, 2000; Sohal, Mockett, & Orr, 2002). Furthermore, DS-AD may be earlier onset (40+ years) than sporadic AD (60+ years) because the overexpression of SOD1 accelerates the formation of superoxide radicals, which act on pre-amyloid to increase Aβ deposition (Harman, 2002).

1.5.3 The intersection between DS and AD

The ‘amyloid cascade hypothesis’ (Hardy & Higgins, 1992) is the prevailing theory as to why people with DS have a higher incidence and earlier onset of AD compared to the typically developing population (Ball et al., 2006). The ‘reserve capacity hypothesis’ (Mortimer, 1988) provides a complimentary account to the ‘amyloid cascade hypothesis’. The two main tenets of the ‘reserve capacity hypothesis’ are: 1. Reserve capacity – remaining functional brain tissue; 2. Threshold – amount of brain tissue required to sustain ‘normal’ cognitive functioning (Mortimer, 1988). The morphology of the DS brain is characterised by, amongst other features: reduced overall cortical volume (Lott, 2010); disproportionately diminished frontal lobes (Aylward et al., 1999); and reduced neuronal density (Lott, 2010). Thus, people with DS are proposed to have a limited ‘reserve capacity’ from birth, which lowers their ‘dementia threshold’. Furthermore, Holland et al. (1998) suggested that the abnormal brain morphology in DS interacts with AD to influence the clinical presentation of the disease. The focus of the differing clinical presentation is compromised frontal lobe functioning in DS (Ball et al., 2006; Ball, Holland, Treppner, Watson, & Huppert, 2008). Indeed, cross-sectional studies of amyloid deposition in DS have found that the striatum is the first effected region, closely followed by the prefrontal cortex (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014).

The frontal lobes mediate functions in three broad domains, which can become compromised with the onset of AD: 1. Cognition – working memory, attention span, executive function; 2. Emotion – apathy, depression; 3. Behaviour – personality changes, inhibitory control. In a prospective, population based study conducted by Ball et al. (2006) it was suggested that early clinical indicators of AD, for participants with DS, were better defined by changes in personality, behaviour and executive dysfunction than decline in episodic memory. In a study of adults with ID, adults with AD-DS presented with comparatively more maladaptive behaviours, such as being excessively uncooperative (Cooper & Prasher, 2002). A longitudinal study of 30 adults with DS, over 16 months, found that adults in the early stages of cognitive deterioration (10) also showed declines in executive function and changes in behaviour (Adams & Oliver, 2010). Together, these findings suggest that frontally mediated processes, such as executive functions, should be focused on when investigating early indicators of AD in DS.

1.5.4 Executive dysfunction in DS-AD

Executive functions (EF) are a family of abilities that make it possible to instigate and maintain purposeful actions. There are three-core executive functions (Diamond, 2013; Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000): 1. Inhibition: behavioral (self-control) and cognitive (selective attention), 2. Working memory, and 3. Cognitive flexibility: set shifting for example. Higher-order abilities such as reasoning, planning, and problem solving are built on these core EFs (Collins et al., 2012; Lunt et al., 2012). The cognitive deficits typically associated with DS can make it difficult to parse the ID from the development of dementia. Indeed, there is some contention as to whether executive dysfunction in this group is developmental, age-related or dementia-related (Ball, Holland, Treppner, Watson, & Huppert, 2008). For example, a comparison between younger adults (<40 years old) with DS and individuals with generalized ID, who were matched for verbal ability, found that the adults with DS were significantly impaired on the EF tasks (Rowe, Lavender, & Turk, 2006). In order to tease out the developmental abnormalities from the clinical progression of DS-AD, Ball and colleagues developed, and/or modified, a battery of neuropsychological tests: the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) (Ball et al., 2006) and, the Executive Function test battery for people with DS (EFDS), which is also known as the Cambridge Executive Functioning Assessment (CEFA) for People with Intellectual Disabilities (Ball et al., 2008).

The CEFA and the Behavioural Assessment of the Dysexecutive Syndrome (BADS-C) were compared to assess their validity as measures of EF in ID, by Willner, Bailey, Parry, and Dymond (2010). The tests (CEFA, BADS-C) were administered to 40 adults with mild to moderate ID, who attended day centres, to find that both had weak relationships with IQ (Willner et al., 2010). However, whilst the BADS-C suffered with floor effects, the CEFA was less affected (Willner et al., 2010). The authors concluded that the CEFA was a suitable measure of EF for adults with mild to moderate ID, whereas the BADS-C had limited utility with this group (Willner et al., 2010). The CEFA, referred to as EFDS for the remainder of the thesis, was chosen as the measure of EF in DS because: 1. Executive dysfunction is one of the earliest indicators of AD in DS (Ball et al., 2006); 2. The EFDS has been independently verified as an appropriate measure of EF for this group (Willner et al., 2010); 3. The EFDS is consistently used by the Dementia in Down's Syndrome research stream at Cambridge, so the continued use in this thesis provides coherence and a platform for between-study comparisons. The EFDS will be discussed in greater details in the general methods section (chapter 2).

Ball, Holland, Watson, and Huppert (2010) conducted a study with 72 adults who had a diagnosis of DS, but not AD. The researchers administered the EFDS, and conducted interviews with the participants' parent or carer. The study found that the majority (95.7%) of participants who were reported to have one (or more) behavioural change(s), also exhibited disinhibited behaviours (Ball et al., 2010). Furthermore, participants' disinhibition score negatively correlated with their performance on three of the EFDS tasks: cats and dogs, Tower of London (ToL), and scrambled boxes (Ball et al., 2010). Of these tasks, performance on ToL and scrambled boxes was related to the number of informant reported changes in personality and behaviour (Ball et al., 2008). The tasks were designed to assess: planning, response inhibition, and working memory functions (Ball et al., 2008). The findings suggest that disinhibition, and executive dysfunction, are early behavioural indicators of the functional decline associated with the development of AD in DS. Furthermore, the prominence of disinhibition in the DS-AD profile supports the hypothesis that the early clinical presentation of the disease is more indicative of frontal-type dementia than typical AD (Ball et al., 2010). Ball et al. (2010) went on to speculate that the behavioural vulnerability to disinhibition suggests that the serotonergically mediated orbito-frontal circuit may be particularly vulnerable to the initial pathology of DS-AD.

Further support for early frontal compromise in DS-AD comes from Adams and Oliver (2010). The authors conducted the Neuropsychological Assessment of Dementia in Individuals with Intellectual Disability (NAID) three times over 16 months. The authors compared the adults with DS who had declined (10), to those who had not (20), to find that adults with cognitive deterioration showed deficits in executive function (Adams & Oliver, 2010). Furthermore, executive dysfunction was: 1. Limited to the decline group, 2. Related to behavioural changes, and 3. Independent of memory decline (Adams & Oliver, 2010). Together, these results suggest that frontal compromise, as indexed by executive dysfunction and behavioural changes, occur early in DS-AD and prior to memory problems.

Nevertheless, there is some resistance to the hypothesis that frontal compromise is the earliest indicator of DS-AD (Blok, Scheirs, & Thijm, 2016; Deb, Hare, & Prior, 2007). This resistance is primarily centred on difficulties in diagnosing AD in DS. Parsing deficits associated with AD, from ID related impairment, is universally agreed as a challenging process (Deb et al., 2007; Nieuwenhuis-Mark, 2009; Sheehan et al., 2015; Strydom et al., 2010; Zeilinger, Stiehl, & Weber, 2013). Deb et al. (2007) uses this difficulty to suggest that DS-AD diagnoses are typically delayed; by which time frontal compromise is detectable, rather than being an ‘early’ symptom. Blok et al. (2016) also argued that adults with DS showed an early compromise of immediate memory, which is comparable to AD development for TD adults. These differing opinions on how AD presents in DS is a result of the difficulties in making a diagnosis and different tools being used, across studies, to do so (Nieuwenhuis-Mark, 2009). This presents a potential confound to be mindful of in the present thesis. Nevertheless, the weight of evidence does suggest that AD presents differently for adults with DS (Ball et al., 2008; Lott & Head, 2001; Nieuwenhuis-Mark, 2009; Strydom et al., 2010), most commonly with frontal dysfunction.

1.6 Synaptic dysfunction

It has been suggest that: “Alzheimer’s disease is a synaptic failure” (Selkoe, 2002). Indeed, the earliest symptoms of AD correlate best with cholinergic and glutamatergic synaptic dysfunction (Davies, Mann, Sumpter, & Yates, 1987; DeKosky & Scheff, 1990; Maurice & Goguadze, 2017; Parsons, Danysz, Dekundy, & Pulte, 2013; Selkoe, 2002; Terry et al., 1991). Furthermore, synaptic dysfunction speaks to early functional, rather than later structural, challenges to the AD affected brain, which is potentially more valuable when identifying therapeutic targets (Selkoe, 2002). The build up of Aβ is linked to synaptic dysfunction, and memory deficits, in that Aβ binds to α-7 nicotinic acetylcholine receptors, which reduces acetylcholine release and consequently the maintenance of long-term potentiation (LTP) (Wang et al., 2000). Figure 1.2 outlines a hypothetical model of how Aβ and synaptic dysfunction interact in AD pathogenesis (Selkoe, 2002).

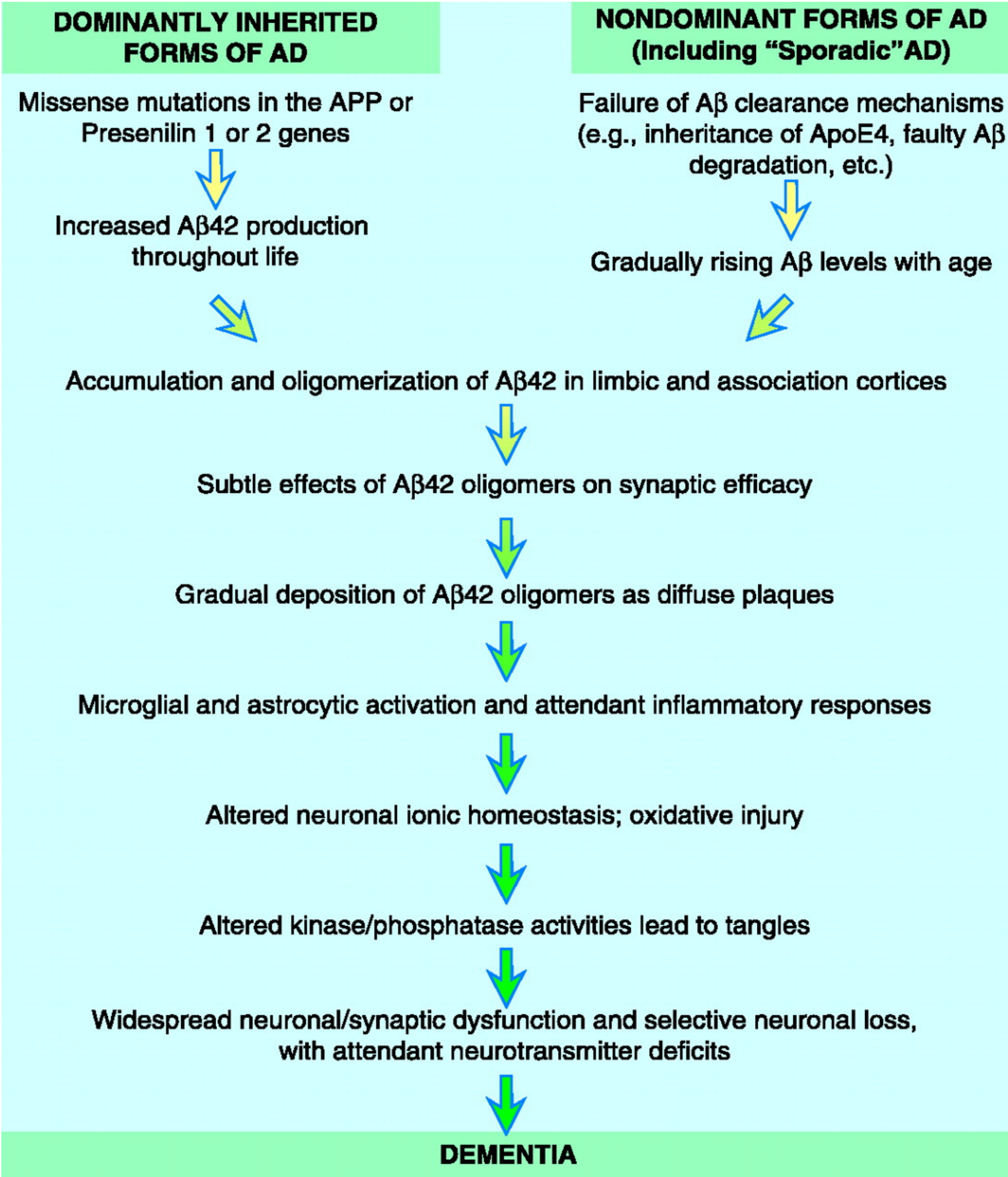

Figure 1.2. "A hypothetical sequence of the pathogenetic steps of AD" from Selkoe (2002).

1.7 Excitability

1.7.1 Hypo- and hyper-excitability in older adults

Even with typical aging, older adults may perform comparatively worse on tasks of episodic memory (Balota, Dolan, & Duchek, 2000) and working memory (Foos & Wright, 1992) than younger adults. This comparatively poorer behavioural performance has been complimented by functional magnetic resonance imaging (fMRI) studies. Some imaging (fMRI) studies with older adults have found that activity is reduced in the left prefrontal cortex (PFC) at the memory encoding stage (Logan, Sanders, Snyder, Morris, & Buckner, 2002) and the medial temporal lobes at the retrieval stage (Cabeza et al., 2004). This “under-recruitment” model has been a popular explanation for the cognitive deficits associated with TD older adults. However, there is also an argument for the effects of “over-recruitment” (Grady, 2008).

“Over-recruitment”, the heightened activity of brain regions, has typically been associated with better task performance. For example, in an fMRI study of a source memory recall task the PFC was engaged bilaterally for higher performing, older adults, whereas younger adults and lower performing older adults showed a right PFC dominance (Cabeza, Anderson, Locantore, & McIntosh, 2002). The suggestion was that lower performing older adults were inefficiently using the same circuitry as they always had, whereas higher performing older adults compensated for their age-related decline by recruiting alternative neural networks (Cabeza et al., 2002). An alternative suggestion is that “over-recruitment” refers to non-selective activity rather than the recruitment of focused alternatives (Logan et al., 2002). Furthermore, older adults may display atypical, increased activity in the PFC because they find the task more taxing than younger adults (Grady, 2008). Consequently, for older adults to succeed at the challenging task they may require greater use of frontally mediated executive functions, which would result in increased PFC activity (Grady, 2008). Furthermore, an fMRI study found that older adults over-recruited fronto-parietal regions when the task was difficult, and performance was low (Spaniol & Grady, 2012). The authors alluded to the over-recruitment being a result of an increased demand, or ineffective use, of cognitive resources, rather than compensatory mechanisms (Spaniol & Grady, 2012). However, it was not possible to qualify this suggestion with the available data (Spaniol & Grady, 2012).

1.7.2 Hyperexcitability and excitotoxicty in AD

Hyper-excitability in pathological aging has been investigated with mouse models of AD. AD is typically associated with the break-down of synapses leading to a decrease in neuronal activity (Busche et al., 2008). An AD mouse model study by Busche et al. (2008), using two-photon Ca^{2+} imaging confirmed that there was decreased neuronal activity in layers II and III of the cortex. However, the authors went on to demonstrate that neurons near the β-amyloid plaques showed increased and spontaneous Ca^{2+} transients (Busche et al., 2008). This excitotoxic response was attributed to a decrease in synaptic inhibition (Busche et al., 2008). At a cortical circuits level, β-amyloid can induce aberrant, excitatory discharge (Palop & Mucke, 2010). In a study of human amyloid precursor protein (hAPP) transgenic mice, Palop et al. (2007) reported that the mice exhibited spontaneous activity in the cortical and hippocampal networks because of excitotoxin challenge. The authors suggested that β-amyloid triggered the aberrant excitation in these regions, resulting in compensatory effects from the inhibitory mechanisms (Palop et al., 2007). In an attempt to reduce over-excitation, the inhibitory circuitry exerted increased restraint over the granule cells and detrimentally constrained the functionality of the excitatory circuits (Palop et al., 2007). In a DS mouse model, the increased inhibition of granule cells resulted in LTP deficits (Kleschevnikov et al., 2004). This finding further supports the hypothesis that the constant limitation of excitotoxic injury with compensatory inhibitory mechanisms can detrimentally impact on neural functionality, including those which serve learning and memory processes (Palop et al., 2007; Palop & Mucke, 2016).

1.7.3 High rates of epilepsy in Alzheimer's disease

Epilepsy is a neurological disorder characterised by excessive, synchronous neuronal activity which manifests as seizures (Fisher et al., 2005). Between 10 and 22% of individuals with AD have at least one unprovoked seizure during the course of their illness (Mendez & Lim, 2003). Furthermore, late-onset epilepsy has been reported in 80% of cases where individuals have DS and AD (Evenhuis et al., 1990; Lai et al., 1989). There are suggestions that the severity of AD is a significant predictor of seizure onset (Amatniek et al., 2006). However, Palop et al. (2009) suggested that the incidence of seizures is independent of disease stage. Therefore, it is unclear as to whether there is a shared or separate aetiology between Alzheimer's and late-onset epilepsy (Noebels, 2011). Individuals who develop AD at a younger age of onset appear to be more susceptible to epileptic seizures than those with late-onset of the disease (Amatniek et al., 2006; Mendez, Catanzaro, Doss, Arguello, & Frey, 1994). Considering that adults with DS have a high prevalence of early onset AD (Evenhuis et al., 1990), epilepsy is an important consideration when working with this group.

1.8 The rising cost of Alzheimer's disease

With rising life expectancy, AD has become a pandemic. Worldwide, over 46 million people are currently living with AD, and this number is expected to double every 20 years (Prince et al., 2015). The global cost of caring for adults with AD will reach $1 trillion US dollars by 2018 (Prince et al., 2015). Despite the staggering economic and emotional strain that the disease poses, only two classes of drugs have been approved for treating the disease: cholinesterase inhibitors (4 from 1993-2001) and NMDA receptor antagonists (1 in 2003). Since 2003, 400 clinical trials have been performed in an attempt to generate more effective treatments, but none have been successful (Cummings et al., 2013). The treatments have primarily targeted Aβ plaques and NFTs of hyperphosphorylated tau peptides; therefore, the drugs are designed to remove these neurotoxic components rather than the regenerate the associated cortical atrophy. As the drugs are primarily tested on adults at the latter stages of the disease, this target imbalance has been suggested as a potential explanation for the wide-spread, trial failures in AD. Consequently, there is now great interest in developing markers for the preclinical stages of AD so that therapeutic interventions, including those for neurotoxic components, can be administered when there is still functionality to be preserved rather than the more challenging task of restoring lost functions (Jackson & Snyder, 2008). Indeed, even modifying the disease progression with a one-year reduction could reduce the number of adults with AD by 9.2 million in 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007).

1.9 Biomarkers of Alzheimer's disease

1.9.1 Definition

The term 'biological marker', commonly referred to as 'biomarker', pertains to "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention" (Biomarkers Definitions Working Group., 2001). This thesis is primarily concerned with evaluating electroencephalography (EEG) as measure of the typical biological process of aging, and as a potential indicator for the pathological development of AD in DS.

1.9.2 Biomarker investigations in DS-AD

The Down Syndrome Biomarker Initiative (DSBI) is a pilot, proof of concept study for deep and frequent phenotyping of adults with DS, with a view to using this model to identify potential markers of AD in DS (Rafii et al., 2015). In that pilot work, the 12 adults with DS (no AD) under went: cognitive testing (including CAMCOG-DS); volumetric magnetic resonance imaging (MRI); amyloid imaging with: position emission tomography (PET) and retinal scans. The participants tolerated the testing regime well, which suggested that the model could be expanded to multi-site testing, in the search for biomarkers of AD (Rafii et al., 2015).

A recent systematic review by Castro, Zaman, and Holland (2016) considered the role of biomarkers in potential prospective preventative treatment trials in DS-AD. The review discussed six classes of potential biomarkers: plasma, cerebrospinal fluid (CSF), positron emission tomography (PET), magnetic resonance imaging (MRI), optical coherence tomography (OCT) and EEG. All of the biomarkers are still at a fledgling stage of research and development but the blood based biomarkers (plasma, CSF), have been most extensively researched in the general population.

In the search for biomarkers of AD, blood plasma studies typically focus on Aβ42/ Aβ40 ratios. Aβ42 is considered a neurotoxic product of APP (Selkoe, 1994). A study of blood plasma samples from 506 adults with DS found that adults with the highest concentrations of Aβ40 and Aβ42 were at highest risk of developing AD (Coppus et al., 2012). Blood plasma samples are typically taken from the arm of participants, by venepucture. Consequently, the Aβ levels apply to the tissues of the body rather than specifically the brain. In comparison, CSF bathes the spine and brain, providing a more targeted reading of Aβ levels in the brain. However, the acquisition of CSF is a much more invasive procedure, which requires a lumbar puncture. A longitudinal assessment of CSF as a biomarker of AD found that adults with mild cognitive impairments (MCI) and the lowest CSF Aβ42 levels (at baseline) were the most likely to transition to AD, within 5 years (Buchhave et al., 2012). Lower CSF Aβ42 levels are believed to reflect an increased retention of Aβ in the brain, which can be imaged by PET as the hallmarks of AD: Aβ plaques (Jack et al., 2010).

Imaging techniques such as PET and MRI are typically used, within an AD biomarker framework, to map the progression of the disease rather than to indicate prodromal stages (Sabbagh et al., 2015). This is because the measures are most informative at the latter stages of the disease: demonstrating the cortical amyloid burden (PET), and the associated cortical atrophy (MRI) (Castro et al., 2016). Recent studies have moved to imaging amyloid in the retina, as an easily accessible extension of the central nervous system, but have yet to correlate the amyloid burden with cognitive decline (Rafii et al., 2015).

EEG has received extremely little attention as a biomarker of DS-AD (Castro et al., 2016). Nevertheless, as early as 1993 it was suggested that cortical slowing in DS adult aging, as measured by quantitative EEG (qEEG), could be used as a model of AD development (Soininen et al., 1993). More specifically, slowing and diminished frequency of the dominant occipital rhythm signals the onset of cognitive deterioration indicative of DS-AD (Menéndez, 2005). Furthermore, qEEG has been tested as a potential diagnostic medium for DS-AD, with a decrease in centroid frequency being a distinguishing factor (from DS no AD) (Salem et al., 2015).

From evaluating dementia research with the typically developing population, Jelic and Kowalski (2009) remain unconvinced about the diagnostic utility of qEEG. Jelic and Kowalski (2009) came to this conclusion by evaluating 46 articles on the subject. The authors conceded that individual studies showed high diagnostic accuracy for dementia and MCI (using qEEG) but the evidence was not sufficient to incorporate this tool into routine clinical practice (Jelic & Kowalski, 2009). In contrast, Jackson and Snyder (2008) were positive about the prognostic potential of electoencephalographical measures: qEEG and event related potentials (ERPs). Jackson and Snyder (2008) came to this conclusion by reviewing articles that had been published on the topic over the previous six years. P300 was highlighted as an ERP with prognostic potential for the transition from MCI to AD (Gironell, García-Sánchez, Estévez-González, Boltes, & Kulisevsky, 2005; Jackson & Snyder, 2008). P600 was highlighted as a potentially useful ERP for indicating the MCI stage, and N400 for mild AD (Jackson & Snyder, 2008). However, unlike P300, both these ERPs (P600, N400) have a strong language component, which could be conflated with ID rather than AD related cognitive impairment. Nevertheless, all of these electroencephalographic measures require more evaluative research to see whether their prognostic potential can be reached.

1.9.3 Evaluation of EEG against biomarker criteria

‘Criteria for establishing a good biomarker for the diagnosis of dementia’ have been set out previously by Humpel (2011, p. 27, box 1). However, the criteria set out by Humpel (2011) were focused on evaluating blood and cerebral spinal fluid biomarkers. Therefore, the present project used a refined and categorised version of the criteria so potential electroencephalographic markers of AD can be evaluated. Please see table 1.1.

Categories	Criteria for establishing a good biomarker for the diagnosis of dementia
Sensitive and specific	Reflect physiological aging processes
	Reflect cognitive measures of AD
	Display high sensitivity to AD, independent of aging effects
	Display high specificity for AD, compared with related disorders
Feasible	Should be measurable in non-invasive, easy-to-perform tests
	Should not cause harm to the individuals being assessed
	Tests should be inexpensive and rapid
	Easy collection of data, not only in hospitals
	Data should be relatively simple and inexpensive to analyse
	Allow measurements repeatedly over time
Scientifically robust	Allow reproducibility in laboratories worldwide
	Changes should be at least two-fold to allow differentiation from controls
	Define good cut-off values to distinguish diseases
	Data published in peer-reviewed journals
	React upon pharmacological intervention

Table 1.1. Criteria for evaluating EEG as a marker of AD for the present project and future investigations. Adapted from ‘criteria for establishing a good biomarker for the diagnosis of dementia’ by Humpel (2011, p. 27, box 1)

1.9.4 The potential for EEG as a biomarker

From a mechanistic perspective, one of the earliest processes in the development of AD is synaptic dysfunction (Busche et al., 2008). This synaptic dysfunction leads to aberrant, excitatory neuronal activity (Palop et al., 2007). The constant, compensatory inhibition of aberrant excitation can reduce neural functionality, including those which serve learning and memory processes (Palop et al., 2007). EEG is a technology which measures, with high temporal resolution, changes in voltage over the scalp resulting from summed postsynaptic potentials in cortical neurons (Teplan, 2002). Therefore, as a coarse measure of neural activity (Luck, 2005), EEG could be an informative biomarker of AD.

Over the past 10 years there have been substantial improvements in the quality of EEG equipment and computing power (Jackson & Snyder, 2008). Consequently, EEG has recently been proposed as a technology with the potential to both delineate preclinical stages of AD and assess the effectiveness of therapeutic interventions, in real-time (Jackson & Snyder, 2008). EEG is a promising candidate for screening preclinical and at risk populations because it is relatively inexpensive, non-invasive and widely available (Poil et al., 2013). EEG also has a widely inclusive clinical utility as some paradigms are passive and thus require limited active participation. Consequently, EEG could be informative about the cognitive impairment of individuals whose neuropsychological tests succumb to “floor effects” or who cannot comply with test demands. Furthermore, EEG as a measure of current cortical activity could potentially contribute to understanding AD progression within the mild, moderate and severe disease categories.

1.10 Electroencephalography

1.10.1 Introduction to EEG

An electroencephalogram (EEG) give a continuous, coarse measure of neural activity (Luck, 2005). From such a continuous recording, neural responses time-locked to specific stimuli can be extracted, and averaged as waveforms (Luck, 2005). These responses are referred to as event related potentials (ERPs). Two features are used to measure ERPs 1. Latency (ms): which is considered an index of processing speed, and 2. Amplitude (µV): which is associated with cognitive resource allocation (Duncan et al., 2009). ERPs can also be characterised by the locus and distribution of the activity at the scalp (Duncan et al., 2009). ERPs can be further characterised by polarity: the voltage difference between the recording and reference electrodes. The predictable generation of ERPs, in response to specific stimuli, provides a non-invasive time-course of cognitive processing in TD adults (Duncan et al., 2009). Consequently, ERPs could be, and have been, informative about cognitive compromise in pathological states (Duncan et al., 2009). The current section will described previous explorations with typical (aging) and abnormal (AD, DS) states with a view to identifying future avenues of research into the nature of AD in people with DS. The general methods chapter (chapter 2) provides more detail on the physiology of EEG recordings, and ERP generation.

1.10.2 Criteria for ERP selection

The criteria for ERP selection in this thesis were: 1. The ERPs have been suggested in previous research to index brain regions and postulated cognitive processes of interest in AD, and 2. The means of recording the ERPs are acceptable and feasible for aging adults with DS. As a result, the ERPs selected for study were mismatch negativity (MMN) and P300 (P3a and P3b components). The rationale for the choices will now be discussed in terms of the ERPs' physiological underpinnings (*section 1.10*), and previous research that has used the ERPs to investigate typical and pathological aging (*section 1.11*), and DS (*section 1.12*).

1.11 ERPs: background

MMN and P3 are well-defined, well-established components which have the operational basis to be applied to clinical disorders (Duncan et al., 2009). N400 and P600 have a similar sound basis, but also contain a language component (Duncan, 2009), which would conflate with the ID in a DS-AD investigation.

1.11.1 MMN

Mismatch negativity (MMN) is an ERP that presents as a fronto-central negativity. MMN is sometimes referred to as N2, N200 or N2a (Duncan et al., 2009). MMN is elicited when an incoming stimulus deviates (is mismatched) from the standard stimuli sequence, within a passive paradigm (Gene-Cos, Pottinger, Barrett, Trimble, & Ring, 2005). MMN is generated bilaterally at the auditory cortices, with some recruitment from the frontal cortex (Giard, Perrin, Pernier, & Bouchet, 1990). The auditory cortex activity reflects the automatic, pre-perceptual component to the potential whereas the frontal recruitment refers to the involuntary shift in attention to the ‘mismatched’ stimuli (Escera, Alho, Winkler, & Näätänen, 1998; Escera, Yago, & Alho, 2001; Giard et al., 1990; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000). MMN is calculated as a difference waveform, by subtracting the average ERP response to standard stimuli from that to deviant stimuli, within 100-250 ms of stimulus presentation (Duncan et al., 2009). MMN reflects the automatic detection of a new, deviant stimulus compared to the sensory memory trace of previous, repetitive stimuli (Duncan et al., 2009).

From a physiological perspective, MMN generation in the auditory cortex is likely the result of repetitive stimulation (standard tones) leading to tonic response inhibition, which is counteracted by deviant (mismatched) stimulation, via glutaminergic mechanisms (Javitt, Steinschneider, Schroeder, & Arezzo, 1996). However, this inhibition hypothesis is limited to simple auditory MMN, and does not explain the MMN response to complex auditory relations or stimuli (words) (Korpilahti, Krause, Holopainen, & Lang, 2001; Obleser et al., 2006; Pulvermüller et al., 2001; Shtyrov & Pulvermüller, 2002).

A predictive coding model would be more explanatory (Strelnikov, 2007), and is expanded on in *section 1.14*.

1.11.2 P300: P3a and P3b

P300 was first described by Sutton, Braren, Zubin, and John (1965) and is perhaps the most studied ERP. P300 is a scalp positivity which can peak anywhere between 250ms and 1000ms but typically peaks at 300ms, as the name suggests (Olichney, Yang, Taylor, & Kutas, 2011). P300 is sometimes referred to as P3 and comprises two potentials: 'P3a' and 'P3b' (Polich, 2007). P3a is the earlier component, which peaks within 200-300 ms of the stimulus, with a fronto-central locus (Squires, Squires, & Hillyard, 1975). P3a is the much lesser studied component. Indeed, in the literature, the term P300 usually just refers to the P3b component, which is maximal over parietal areas (Polich & Kok, 1995). The scalp-wide presence of P300 (Soltani & Knight, 2000) has lead to the suggestion that the potential either has several independent generators, or reflects the central integration of wide-ranging connections (Duncan, Kosmidis, & Mirsky, 2003; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Pineda, Foote, & Neville, 1989). Nevertheless, the foci of P300 generation have been suggested as the: hippocampus, superior temporal sulcus, ventrolateral prefrontal cortex, and potentially the intraparietal sulcus (Halgren et al., 1995; Halgren, Marinkovic, & Chauvel, 1998; Kiss, Dashieff, & Lordeon, 1989; Smith et al., 1990).

P300 is the electrophysiological response to detecting an 'oddball', target tone which breaks a sequence of repeated, 'standard' tones. P3a is seen in response to rare or novel events, whereas P3b requires attentive, evaluative and categorical processes to be elicited in response to a deviant tone (Duncan et al., 2009; Johnson & Donchin, 1978). The amplitude of P300 is enhanced by salience (Yeung & Sanfey, 2004), and diminished by excessive repetition (Squires, Wickens, Squires, & Donchin, 1976). The P3a component is considered to be the evaluative response to novelty (Friedman, Cycowicz, & Gaeta, 2001). The P3b is generally considered to be an index of cognitive processes required in the maintenance of working memory and the allocation of attentional resources (Polich & Kok, 1995).

From a physiological perspective, several neurotransmitter systems are involved in the generation and modulation of P300 (Hansenne, 2000). P300 amplitude is increased by noradrenergic agonists (Pineda & Swick, 1992) and/or, in a biphasic relationship, decreased by dopaminergic agonists (Stanzione et al., 1991). Conversely, P300 amplitude is decreased by cholinergic antagonists (Hammond, Meador, Aung-Din, & Wilder, 1987) and gabaergic agonists, which also increases P300 latency (Meador, 1995).

1.12 ERPs: typical and pathological aging

1.12.1 MMN

MMN can be viewed as a means of indexing auditory sensory memory traces (Pekkonen et al., 1996). The relationship between MMN and aging is elucidated as declines in sensory memory and perceptual accuracy relate to both factors (MMN, older adults) (Demiral, Malcolm, & Henderson, 2012; Fakhri, Sikaroodi, Maleki, Ali Oghabian, & Ghanaati, 2012; Lauzière, Dubois, Brière, & Nadeau, 2012; Stewart & Wingfield, 2009). Studies have suggested that the age effect on MMN is isolated to an amplitude decrease (Pekkonen et al., 1996; Pekkonen, 2000; Schiff et al., 2008). Indeed, MMN seems to succumb less to aging effects than later, more cognitive components, like P3b (Schiff et al., 2008).

MMN amplitudes decrease with age (Alain, McDonald, Ostroff, & Schneider, 2004; Alain & Woods, 1999; Bertoli, Smurzynski, & Probst, 2002, 2005; Cooper, Todd, McGill, & Michie, 2006; Czigler, Csibra, & Csontos, 1992; Horváth, Czigler, Birkás, Winkler, & Gervai, 2009; Horváth, Czigler, Winkler, & Teder-Sälejärvi, 2007; Karayanidis et al., 1995; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Pekkonen et al., 1996; Pekkonen, 2000; Rimmele, Sussman, Keitel, Jacobsen, & Schröger, 2012; Schiff et al., 2008; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015; Woods, 1992), but are significantly smaller still for adults with AD compared to age-matched controls (Kazmerski, Friedman, & Ritter, 1997; Pekkonen, 2000). However, the strongest responses to deviant auditory stimuli are elicited fronto-centrally and as such MMN has been suggested as a valuable indicator of front-temporal dementia (Hughes & Rowe, 2013). The early behavioural presentation of AD in DS appears to be weighted towards changes in cognitive functions underpinned by the frontal lobes (Ball et al., 2006; Ball, Holland, Treppner, Watson, & Huppert, 2008). As such, the initial presentation of DS-AD is more akin with fronto-temporal dementia than typical AD (Ball et al., 2006). Therefore, it would be relevant to investigate age and AD related changes in DS by using paradigms which elicit fronto-centrally distributed ERPs.

1.12.2 P300: P3a and P3b

With typical, adult aging, P300 has been shown to decrease in amplitude and increase in latency (Duncan et al., 2009; Kerr, van Albada, Rennie, & Robinson, 2010; Polich, 2007; Rossini, Rossi, Babiloni, & Polich, 2007; Schiff et al., 2008; Walhovd, Rosquist, & Fjell, 2008). The physiology behind this relationship has been linked with: 1. The volumetric changes to brain regions (fronto-temporal, hippocampus), which support P300 generation, with typical aging (Fjell, McEvoy, Holland, Dale, & Walhovd, 2013), and 2. The typical decline in functions indexed by P300: attention and memory (Quigley, Andersen, Schulze, Grunwald, & Müller, 2010; Quigley & Müller, 2014). Again, the literature is generally referring to the P3b component when the term P300 is used. However, frontal lobe functioning is potentially less efficient for older adults (Fabiani, Friedman, & Cheng, 1998). Furthermore, a topographical study of P300 distribution found that, with age, sources move to have a frontal distribution, and the maximum intensities gain a temporal locus (Tsolaki et al., 2015). These topographical findings present an argument for whole brain, rather than single canonical electrode, analyses when exploring the relationship between the ERPs and typical aging.

The ERP P300 (P3) has been used frequently and successfully to disambiguate AD from typical aging in the general population and as such has been selected for this project. P300 elicited under a standard, auditory oddball paradigm is one of the most commonly used ERPs to investigate AD (Ally, Jones, Cole, & Budson, 2006). The studies have generally suggested that cognitive decline in AD is reflected in longer P300 latency times (Gungor et al., 2005; Jiménez-escrig et al., 2002; Lai, Lin, Liou, & Liu, 2010), and reduced P300 amplitudes, compared to age-matched controls (Ally et al., 2006; Caravaglios, Costanzo, Palermo, & Muscoso, 2008; Gungor et al., 2005; Lee et al., 2013). Again, references to P300 in the literature are typically referring to the P3b component.

A meta-analysis of 48 studies which compared auditory P300 latency between TD adults, and adults with MCI (8/48) or AD (40/48), was conducted by Howe, Bani-Fatemi and De Luca, (2014) with a view to evaluating the preclinical diagnostic value of P300 latency for MCI and AD. The meta-analysis was launched because although previous studies have been predominantly positive about the utility of P300 latency in AD research, some studies have failed to find a significant relationship between the two (Ashford, Coburn, Rose, & Bayley, 2011; Lee et al., 2013). The meta-analysis concluded that P300 latency was a useful tool in clinical, AD research but more studies were required to confirm the usefulness at the MCI stage (Howe et al., 2014).

Using typical EEG recording and analysis methods, the sensitivity and specificity of P300 to AD have been reported in the literature, with high variation, at between 50% (Gironell et al., 2005) and 80% (Karim Bennys, Rondouin, Benattar, Gabelle, & Touchon, 2011). The conventional methods referred to are ERP waveform averaging from single electrode sites (Pz for example). However, recent studies which have employed more sophisticated methods, such as dipole source analysis and topographical scalp maps, have improved sensitivity and specificity to >80% (Bonanni et al., 2010; Frodl et al., 2002; Juckel et al., 2008). Indeed, sensitivity has been reported at as high as 90% (Frodl et al., 2002), and specificity at 97% (Bonanni et al., 2010). Sensitivity and specificity to the dementia-type (AD) is essential from a biomarker perspective (Humpel, 2011). The meta-analysis also highlighted how P300 research in AD has predominantly focused on the P3b component, and the contributions of P3a have been overlooked (Howe et al., 2014) and are little understood (Polich, 2007). These assertions have informed the methodological and research focus (P3a) choices in this thesis.

1.13 ERPs: a systematic review of previous DS studies

1.13.1 Literature search

A systematic review was conducted to explore mismatch negativity (MMN) and P3 (P3a, P3b), in relation to DS. The review used the search terms and inclusion pathway outlines in figure 1.3 (*1.12.2. The article identification process*). The PubMed, Scopus and Web of Science databases were searched in order to identify all published articles about the ERPs (MMN, P3) and DS. In an attempt to be fully inclusive, all of the synonyms for mismatch negativity (MMN, N2, N200, N2a) and P3 (P300, P3a, P3b) were searched. Nevertheless, the literature on the ERPs (MMN, P3) and DS is scarce, as only 30 unique results were found. Of the search results, the review only included original ERP (MMN, P3) studies, which were written in English, and recruited children or adults with DS. Studies were predominantly excluded when DS was referred to but not tested as a participant group. Consequently, only 16 articles were appropriate for full review. The full list and summary of the articles can be found in table 1.2 (1.13.3. *The articles* identified), and the review in section *1.13.4. Summation and review of the identified articles*.

1.13.2 The article identification process

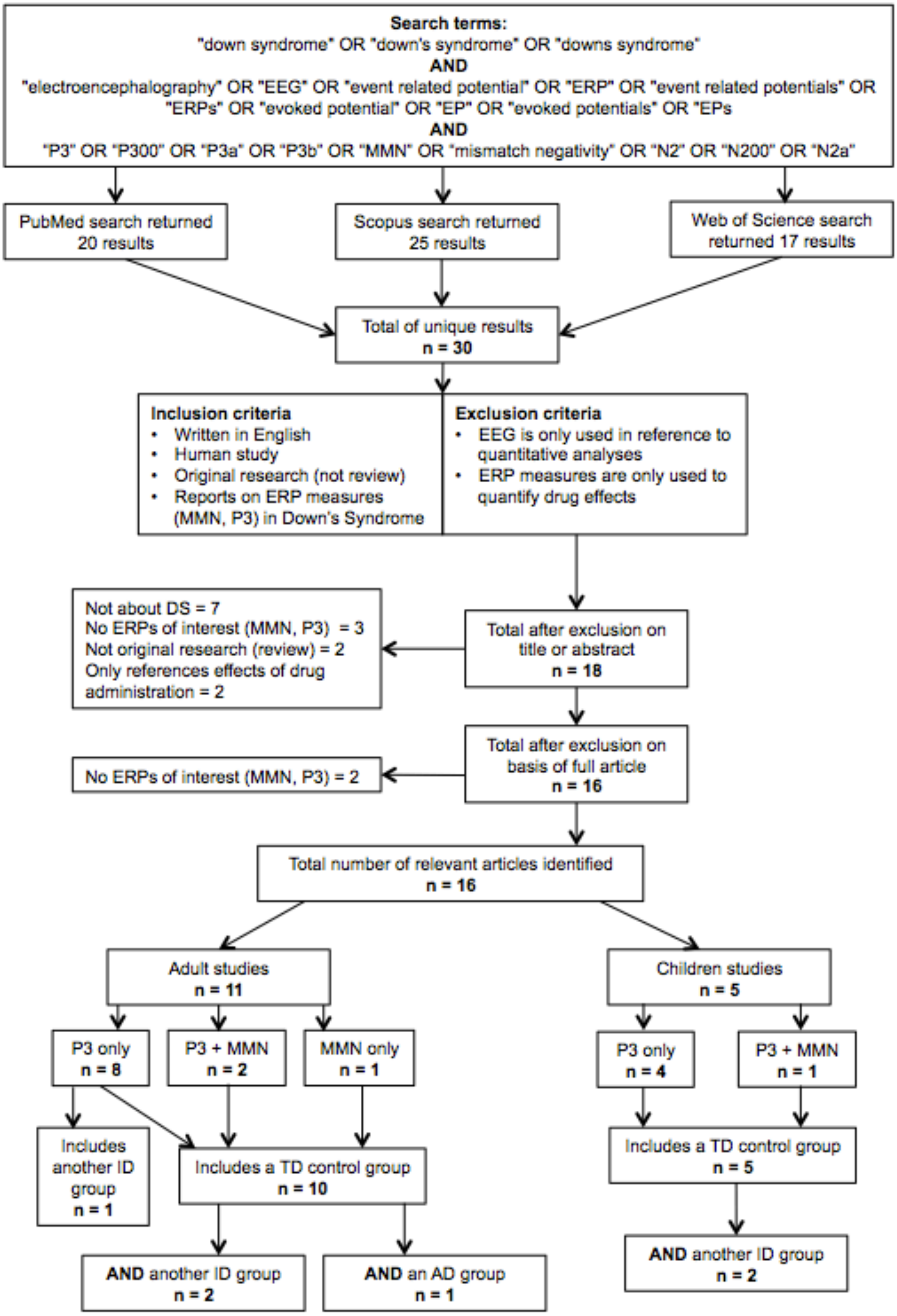

Figure 1.3. The article identification process for a systematic review of event related potentials (ERPs): MMN and P3, in Down's Syndrome (DS). The literature search was carried out on 6th February 2017. TD = typically developing, ID = intellectual disability, AD = Alzheimer's disease.

1.13.3 The articles identified

Author	Sample	ERP Measures	Key Findings 1/3
Arisi et al. (2012)	15 adults with DS (16-38 yrs, 7 males) 16 age-matched TD controls (7 males)	N1, **N2 (MMN),** P1, P2	Adults with DS, and normal hearing thresholds, showed longer latencies than controls, across the measures. N2 was only present in 14 DS and 14 TD.
Blackwood et al. (1988)	89 adults with DS (16-66 yrs), including 16 with DS-AD 29 adults with fragile X syndrome 83 TD adults (Abstract only)	**P300**	P300 latency increased at (approximately) 37 years old for adults, and at 54 years old for control participants. The 16 adults with DS-AD drove the premature latency increase.
César, et al. (2010)	17 adults with DS (18-39 yrs, 10 males) 34 TD controls (18-39 yrs, 20 males)	N1, P2, **N2**, **P3**	Adults with DS showed longer latencies on all the measures and smaller amplitudes for N2-P3.
Díaz & Zurron (1995)	12 children with DS (mean 14.16 yrs) 12 TD controls (mean 14.58 yrs)	SAEP, MAEP, LAEP: N1, P2, **N2, P3**	Relative to control participants, the N2 and P3 latencies were longer in DS. The N2-P3 amplitude decreased with successive blocks for controls. However, the N2-P3 amplitude was constant in DS, until the fourth block where the amplitude rose.
Kakigi, et al. (1994)	47 adults with DS (18-48 yrs, M = 30.8 yrs, 26 males) 37 adults with AD (60-82 yrs, M = 68.5 yrs, 15 males) 43 younger TD controls (22-53 yrs, M = 30.8yrs, 17 males) 20 older TD adults (60-78yrs, M = 69.1yrs, 10 males)	**P300**	Only 24 adults with DS showed consistent ERPs, of which there was a delayed and frontal shift to the P300. This frontal shift was not present in the AD or TD (younger, older) participants.
Kaneko, et al. (1996)	18 children with FAS 18 children with DS 18 TD children Total of 54 children (4-15 yrs, M = 9.1 yrs)	**P300**	The children with FAS and DS showed significantly longer parietal P300 (P3b) latencies than TD children. Furthermore, the amplitude of the frontal P300 (P3a) was significantly larger for DS than FAS or TD children.

Author	Sample	ERP Measures	Key Findings 2/3
Kazan et al. (2016)	17 children with DS (7-15 yrs, M = 10.9 yrs, 8 males) 21 TD (7-15 yrs, M = 9.8 yrs, 5 males)	BAEP, **P300**	With a quantitative analysis, there were no statistically significant differences in P300 latencies between the groups. With a qualitative analysis, 33% of DS children showed increased P300 latency.
Lalo, et al. (2005)	20 adults with DS (18-31 yrs, M = 24 yrs, 10 males) 20 TD adults (19-31 yrs, M = 25 yrs, 10 males)	N1, P2, **N2a (MMN),** N2b, **P3a, P3b**	P3b was present in 55-65% of adults with DS, compared to 75-85% of controls, and was longer in latency. For control participants, MMN was present for most and P3a for half. In contrast, the presence of all three ERPs (P3a, P3b and MMN) in DS was as low as 10-25% of participants.
Medaglini et al. (1997)	45 adults with DS (M = 30.6 yrs, 16 males) TD controls (Abstract only)	N1, P2, N2, **P3,** qEEG	Adults with DS showed longer latencies and smaller amplitudes of P300 than controls. Within group (DS), P300 latency and amplitude differences did not distinguish young from old, and AD from no AD. P300 latencies were abnormal (>2.5 SD) in 47% of cases.
Miezejeski et al. (1994)	80 males: 13 with DS, 23 with generalised ID, 44 TD controls (Abstract only)	**P3**, P5	Adults with DS and control participants had comparable P3 latencies, but shorter latencies than adults with generalised ID.
Muir et al. (1988)	65 adults DS 20 adults fragile X (Abstract only)	**P300**	Over the course of two years, 14% of the adults with DS developed AD. Of those who developed AD at follow-up, 78% showed an increase in P3 latency of 3 standard deviations above the group mean.
Niwa, et al. (1983)	4 children with DS (11-17 yrs, M = 15yrs, 1 male) 4 children with autism (12-17 yrs, M = 14.1yrs, 4 males) 5 TD children (11-22yrs, M = 17 yrs)	**P300**	Participants with autism showed significantly lower P300 amplitudes than the other groups (DS, TD). The DS and TD groups showed similar P300 amplitudes. The latencies did not significantly differ between groups.

Author	Sample	ERP Measures	Key Findings 3/3
Seidl et al. (1997)	10 children with DS (11-20 yrs, M = 15 yrs, 6 males) 10 age- and gender-matched TD controls (M = 15.1 yrs) Antihistaminergic treatment group: 12 TD adults (20=28 yrs, 6 males)	N1, P2, N2, **P3**	Participants with DS showed longer latencies for N1, P2, N2 and P3. The mean P3 amplitude at Cz was smaller in DS than TD, but not significantly. Between testing blocks the P3 amplitude decreased for TD participants but remained constant for DS participants. For the antihistaminergic treatment group, pheniramine administration increased P3 latency and maintained P3 amplitude during repeated stimulation. These findings implicate the histaminergic system in the modulation of P3.
St. Clair & Blackwood (2013)	101 adults with DS (16-66 yrs) 88 TD controls (18-75 yrs)	N100, P200, **P300**	P300 waveforms were obtained from 90 adults with DS and 85 TD controls. For adults with DS, P300 latencies were significantly longer, and P300 amplitudes significantly smaller, than TD controls. P300 latencies increased with age for both groups, however the intercept for age-related change was 37yrs for DS and 53 yrs for TD.
Vieregge, et al. (1992)	14 adults with DS (22-42 yrs, M = 32 yrs, 5 males) 18 younger TD controls (22-26 yrs, M = 24 yrs, 5 males) 20 older TD controls (55-87 yrs, M = 67 yrs, 8 males)	N1, P2, N2b, **P3**	P3 latencies were longer for adults with DS than the younger and older TD controls. The P3 amplitude was similar in DS and younger controls, but larger than older controls. However, for adults with DS, there was an amplitude shift towards positivity, across the measures, and with a fronto-central focus. For adults with DS, P3 did not correlate with age or cognitive test performance.
Wetter & Murphy (1999)	20 adults with DS (M = 26 yrs, SD = 10) 20 age-matched TD controls	N1, P2, N2, **P3**	Adults with DS showed longer P3 latencies than controls. Adults with DS and cognitive decline showed longer latencies than adults with DS but no AD components.

Table 1.2. Studies on the ERPs (MMN, P3) in DS. Abbreviations: ERP = event related potential, M = mean, SD = standard deviation, DS = Down's Syndrome, TD = typically developing, ID = intellectual disability, FAS = foetal alcohol syndrome, yrs = years, BAEP = brainstem auditory evoked potentials, SAEP = short latency auditory evoked potentials, MAEP = middle latency auditory evoked potentials, LAEP = late latency auditory evoked potentials. The potentials in bold are those which were analysed in the article and were of interest (MMN, P3) for the review. The key findings pertain to the measures of interest (MMN, P3). The potentials are listed as they were written in the text. MMN can also mean N2a, and sometimes N2 (depending on the time period used in the text). P3 can also mean P300, and be referring to the P3a or P3b component.

1.13.4 Summation and review of the identified articles

Across the studies, P3 was predominantly presented to have longer latencies for adults and children with DS, than TD control participants (Blackwood et al., 1988; César, Caovilla, Munhoz, & Ganança, 2010; Kakigi, Neshige, Matsuda, & Kuroda, 1994; Lalo, Vercueil, Bougerol, Jouk, & Debû, 2005; Medaglini et al., 1997; Seidl et al., 1997; St. Clair & Blackwood, 2013; Vieregge, Verleger, Schulze-Rava, & Kömpf, 1992; Wetter & Murphy, 1999). However, DS P3 latencies were shorter when compared to children with foetal alcohol syndrome (FAS) (Kaneko, Ehlers, Philips, & Riley, 1996), and adults with generalised intellectual disability (ID) (Miezejeski, Heaney, Belser, & Sersen, 1994). In three cases, the P3 latencies in DS were presented as comparable to TD children and adults (Hellen Medeiros Kazan et al., 2016; Miezejeski et al., 1994b; Niwa, Ohta, & Yamazaki, 1983), and children with autism (Niwa et al., 1983). However, Kazan et al. (2016) presented a discrepancy between quantitative and qualitative analyses of P3 latencies. In a quantitative analysis, 17 children with DS presented with similar P3 latencies to 21 TD children. In contrast, a qualitative analysis revealed that a third of the children with DS showed increased P3 latencies (Kazan et al., 2016). This discrepancy ties into a larger research issue of considering a heterogeneous disorder (DS), which encompasses a wide range of intellectual ability and disability, as a homogenous group.

P3 latency was linked with the hypothesis of premature aging in DS for two studies: Blackwood et al. (1988) and St. Clair & Blackwood (2013). The studies found that the intercept for age-related increase to P3 latency was 37 years for adults with DS and 53 years for TD controls (Blackwood et al., 1988; St. Clair & Blackwood, 2013). However, Blackwood et al. (1988) went on to suggest that the 16 adults with DS-AD might have driven the premature latency increase. A link between increased P3 latency, aging and DS-AD was presented in a 2-year, longitudinal study of adults with DS that suggested of those (14%) who transitioned to AD, 78% showed a significant increase in P3 latency (Muir et al., 1988). A comparison of DS and AD, as individual disorders, indicated that the locus of P3 was shifted frontally for adults with DS but not for TD adults, with and without AD (Kakigi et al., 1994).

There were discrepancies between the studies that compared P3 amplitudes between participants with DS and TD controls. Two adult studies suggested that P3 amplitude was significantly smaller for participants with DS than TD controls (César et al., 2010; St. Clair & Blackwood, 2013), whereas a study of children suggested that the amplitudes were similar between groups (Niwa et al., 1983). Further studies of children with DS presented that P3 amplitudes did not habituate and diminish (remained constant) across trials (Díaz & Zurron, 1995; Seidl et al., 1997), and would even increase on the final round (Díaz & Zurron, 1995), or be generally larger than they were in TD and FAS children (Kaneko et al., 1996). Kaneko et al. (1996) suggested that the larger P3 amplitude was specifically a frontal P3 (P3a), which ties into other observations of a frontal shift in the P3 locus for adults with DS (Kakigi et al., 1994; Vieregge et al., 1992). The rationale for an enlarged frontal P3 (P3a) was presented as 1. A disturbance in generating a P3b response (Kakigi et al., 1994), 2. A failure to habituate, and inhibit, at an electrophysiological level (Díaz & Zurron, 1995), and 3. A potential product of accelerated aging in DS (Kakigi et al., 1994). This finding is predominantly driven by child studies using 10-year-old EEG acquisition and analysis techniques. The research should be developed, beyond single electrode analyses, to a group (adults) that can speak to the relationship between P3, premature aging and AD development.

Similar to the AD literature, the ERP studies in DS studies have been predominantly focused on the P3 potential. Indeed, only one study (Arisi et al., 2012) discussed MMN in the absence of P3 findings. The few studies which referenced MMN spoke of increased latencies and reduced amplitudes (Arisi et al., 2012; César et al., 2010; Lalo et al., 2005). The paucity of research on this potential presents a need for more investigations, using up-dated techniques.

1.14 Predictive coding

Predictive coding utilises the economical assumption that the majority of sensory cues from the environment are repetitive and therefore redundant (Jack & Hacker, 2014). This top-down assumption: ‘prediction’, is used to constrain processing of bottom-up, sensory inputs (Friston, 2005). The processing is constrained to only those which defy the assumption: ‘prediction errors’ (Friston, 2005). This economical, hierarchical framework can be used to contextualise ERPs (MMN, P3a, P3b) as ‘prediction errors’ (Garrido, Kilner, Kiebel, & Friston, 2007; Lieder et al., 2013; Wacongne et al., 2011). In the absence of attention, the processing of prediction errors occurs at a low-level, producing MMN and P3a waveforms (Bekinschtein et al., 2009). A pattern is extracted when these low-level, ‘local’ violations are processed at higher-levels (Chennu, Noreika, et al., 2013). This pattern extraction uses environmental cues to improve the quality of the top-down predictions (Chennu, Noreika, et al., 2013). This is an iterative process: low-level, ‘local’, environmental cues inform higher-level, ‘global’ predictions; these predictions are then used to constrain processing from the lower levels (Chennu, Noreika, et al., 2013). When attention is engaged and violations occur at this higher ‘global’ level of processing then a P3b waveform is generated (Bekinschtein et al., 2009). This distinction in prediction error processing can be used to delineate ‘local’ (MMN, P3a) and ‘global’ (P3b) components, within the same odd-ball paradigm: the global-local paradigm (Bekinschtein et al., 2009). The global-local paradigm was developed by Bekinschtein et al. (2009) and forms the basis of this thesis. The paradigm is described in detail in the general methods (chapter 2, 2.15).

1.15 Rationale

The predictable high risk of AD in DS presents a considerable burden for this aging population. The highest risk for AD development is age, rendering age as an unavoidable consideration in any investigation of AD. The reactive rather than preventative administration of AD treatments has thus far gleaned poor results; so treatment development is now moving towards testing at prodromal stages. Consequently, identifying individuals who will develop AD, and when they will develop it, has never been more important. Furthermore, the efficacy of preventative treatments needs to be tested in real time, rather than waiting 20 years to see if someone develops the disease. With these observations, the development of appropriate biomarkers of ‘who’ and ‘when’ AD will develop, has gained significant interest. Older adults with DS develop the pathology of AD with inevitability. Having identified the ‘who’, it is now important to predict ‘when’. In order for a biomarker to be usable as a widespread tool, it must be easy to administer, relatively inexpensive and non-invasive. As such, EEG has garnered some attention as a marker of AD in the TD population. The ultimate aim of this thesis is to evaluate ERPs as potential predictors of the cognitive decline associated with DS-AD. The thesis will build on each chapter in an attempt to achieve this aim: Firstly, as DS is associated with atypical brain morphology, the extent to which the ERPs differ from age-matched TD controls will be established. Secondly, the ERPs will be considered in terms of the highest AD-risk factor: age, with a view to exploring the premature aging hypothesis of DS. Thirdly, the ERPs’ relationship with neuropsychological measures, associated with early DS-AD development, will be explored. Finally, a preliminary exploration of whether the ERPs can predict cognitive decline, a year later.

1.16 Thesis aims

The overall aims of the study are as follows, and are explored in the four findings chapters:

1. To use electroencephalographic measures (MMN, P3a, Pb) to compare adults with Down's Syndrome and typically developing controls, within a predictive coding framework (*chapter 3*).

2. To use electroencephalographic measures as a means of testing the accelerated brain aging hypothesis in Down's Syndrome (*chapter 4*).

3. To explore whether electroencephalographic measures relate to a range of neuropsychological measures, that have been reported to be sensitive to the functional decline associated with the early stages of Alzheimer's disease in Down's Syndrome (*chapter 5*).

4. To investigate the potential value of electroencephalographic measures as predictors of cognitive decline in adults with Down's syndrome (*chapter 6*).

2 Chapter 2. General methodology

2.1 Introduction

The methodologies used in data collection and analyses for the study are described in this chapter. The subsequent data chapters (chapter 3,4,5) all share methodologies relating to participant recruitment and assessments. The data chapters (3,4,5,6) also share methodologies for data collection and pre-processing of the electrophysiological data. Therefore, the subsequent data chapters will only describe deviations to the general methodology that are relevant to the specific subject matter of the chapter.

2.2 Approvals from Regulatory Authorities

Ethical approval to conduct the study (reference 14/LO/1411) was provided by the Queen Square National Research Ethics Service (NRES) on 08.09.14. The committee had the expertise to assess studies aiming to include individuals who may lack the capacity to consent to participation. Following favourable ethical opinion, the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) Research and Development office (R&D) approved the study on 10.10.14. The study was enacted within the ethically approved protocol and the CPFT R&D governance framework. Confirmation of the study's ethical approval can be found in appendix A.

2.3 Design

A schematic of the testing schedule is provided in figure 2.1 and expanded upon below.

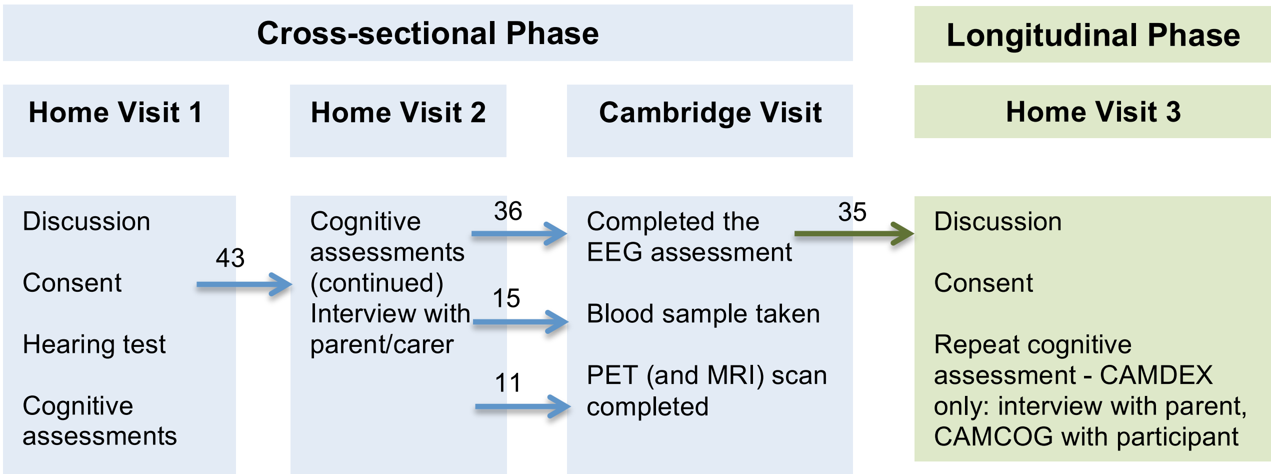

Figure 2.1. A schematic of the study design: left to right is the chronological order of the study, the blue sections are cross-sectional, and the green are longitudinal. The numbered arrows denote the number of participants who transitioned from one phase of the project to the next. The numbered arrows from 'Home Visit 2' to 'Cambridge Visit' indicate that 36 participants completed the EEG assessment, of whom 15 successfully had blood samples taken and 11 had PET (and MRI) scans. 35 of these participants transitioned to the 'Longitudinal Phase'.

The study was composed of two phases:

Cross-sectional phase: men and women with Down's Syndrome (DS) aged 20+ years old (aiming for approximately 10 participants per decade), and age- and gender-matched controls from the typically developing (TD) population, were recruited for neuropsychological and electrophysiological assessments. The work comprising the cross-sectional phase of the research is described in three chapters. In chapter 3, the electrophysiological measures were compared between adults with DS and TD controls. In chapter 4, the effect of age on the electrophysiological measures was explored both within and between groups (DS, controls). In chapter 5, the relationship between the neuropsychological and electrophysiological assessments was explored.

Longitudinal phase: at the first assessment period there were neuropsychological and electrophysiological testing components, as described in sections 2.8 and 2.14, respectively. Between 9 and 14 months after the first assessment period all the participants with DS were invited for a repeat neuropsychological assessment. The purpose of the repeated neuropsychological assessment was to explore whether the initial electrophysiological assessment had predictive value for any cognitive decline observed between the first and the second assessments (chapter 6).

2.4 Collaborations

This study is part of a larger ‘Defeat Dementia in Down’s Syndrome’ research stream in the Cambridge Intellectual and Developmental Disabilities Research Group (CIDDRG), which is composed of several studies. The amyloid imaging study (11/EE/0348) and the mitochondrial function study (12/EE/0249), were the primary source of participant recruitment for the present study. The PET data was collected and processed at the Wolfson Brain Imaging Centre (WBIC) by researchers on the amyloid imaging study: Dr Tiina Annus and Mr Liam Wilson, University of Cambridge. Dr Young Hong and Dr Tim Fryer performed the kinetic modelling and reconstruction of the PET data at the WBIC, University of Cambridge. An eye imaging study (14/EE/118) ran concurrently with the present study so some cross-sectional neuropsychological testing was shared with Miss Madeleine Walpert. Some longitudinal neuropsychological testing was shared with Miss Paula Castro, a research intern. The electroencephalographic assessments and analyses methods were developed in collaboration with Dr Srivas Chennu, Dr Tristan Bekinschtein and Dr Valdas Noreika, at the University of Cambridge.

2.5 Participants

2.5.1 Identification

The participants with DS were predominantly identified from their previous participation in studies run by the ‘Defeat Dementia in Down’s Syndrome’ research stream in CIDDRG. Only participants with DS who consented to being approached for future studies were identified for the present study. The subset of participants with DS who had not taken part in previous CIDDRG studies were identified through charities, predominantly the Down Syndrome Association (DSA). The DSA, and a local support charity for people with intellectual disability (ID) called Eddies, were also encouraged to advertise the research group’s open days. The primary reason for the open days was to involve previous participants and interested members of the public in our research findings and plans. People with DS who expressed interest in taking part in research at the open days left their contact details and were later contacted with study specific information and the opportunity for a home visit, to further explain what participation involves. Participants with DS were identified for the longitudinal phase by virtue of having been involved in the cross-sectional phase of the project, and having agreed to be contacted about future studies. Ethical approval was gained to recruit through: NHS services, predominantly local learning disability community teams; Cambridgeshire and Peterborough Foundation Trust (CPFT) clinicians and Participant Identification Centres (PICs). However, no participants were recruited through this avenue.

The age- and gender-matched typically developing controls were initially recruited through advertisements in: public libraries; job centres; University of Cambridge buildings, predominantly the Department of Psychiatry, Department of Experimental Psychology and Addenbrooke’s Hospital. To attract a wider range of control participants, ‘Join Dementia Research’ (JDR) was also used. JDR has a database of individuals who are interested in taking part in research. A JDR administrator contacted individuals, by email, who lived within a 50-mile radius of Cambridge and matched the inclusion criteria for the study. People who were potentially interested in participating made contact with the researcher by phone or email, using the contact details on the advertisement, to express an interest in taking part.

2.5.2 Approach

Potential participants with DS who agreed, or whose carers and consultees agreed, to be contacted by the research team were sent an information pack about the study which included: a covering letter that introduced the study, information sheets for the participant and carer, and a reply slip.

Potential participants for the age-matched, typically developing control group contacted the research team directly to discuss the study. The potential participants were then presented with an information sheet, which explained the study in more detail and were encouraged to ask the researcher questions.

2.5.3 Recruitment and informed consent

Adults with DS are a potentially vulnerable group, especially when any intellectual disability is compounded by a dementia diagnosis. Consequently the informed consent process and capacity to consent concerns were thoroughly and carefully addressed. The informed consent process was delivered in line with the provisions of the *Mental Capacity Act 2005* where participants demonstrated understanding, retaining, weighing and communicating their decision to take part in the study. The informed consent process for the study is fully described in the following paragraph.

Potential participants with DS who agreed to receive information about the study found enclosed within that information pack a reply slip. The potential participant, or their carer, to indicate their interest in participating and to provide the name and telephone number of the ‘person that knows them best’, filled out the reply slip. The research team then called the ‘person that knows them best' to organise when a researcher could visit them at their home, or another convenient location. During this visit the researcher further discussed the study with the potential participant and the 'person that knows them best'. The researcher explained the study using materials that were composed of pictures, made in Widgit, and simple language to maximise understanding and thus capacity to consent to the study. Participants were asked questions about the study information to assure the researcher of their understanding. Previous experience from research at CIDDRG has suggested that many people with DS have the capacity to consent to participating in studies, provided that the study information is made accessible. However, provision was made for those potential participants who lacked the capacity to consent to participating in the study. In such cases a person able to act on behalf of the potential participant, most likely the 'person that knows them best' with whom we would have already been liaising, was approached as their personal or nominated consultee. The consultee was asked to form an opinion as to whether or not the potential participant would have objected to participating in the study. The assent of the participant was always required. So if at any point the participant indicated, either verbally or with aversive body language that they wished to be withdrawn from the study then they were. The process was repeated for the longitudinal phase. Only one participant was recruited through the consultee process.

The potential age- and gender-matched typically developing controls used the research team's contact details listed on the advertisement to express an interest in participating. The potential participants were then provided with more information about the study and the opportunity to discuss the study with a researcher. These measures were considered adequate for the controls to give informed consent.

All of the information materials and consent forms can be viewed in the appendices B-P.

2.5.4 Inclusion and exclusion criteria

Inclusion Criteria

- At least 20 years of age
- Clinically diagnosed Down's Syndrome (for the DS group)
- Typically developing and age-and gender-matched to the Down's Syndrome group (for the controls)

Exclusion Criteria

- Unable to indicate hearing tones delivered at 1000Hz and 3000Hz at 55dB by the Siemens HearCheck Screener, which is a portable system
- Have active, or history of, schizophrenia themselves or in first-degree relatives
- Evidence on cognitive screening of mild cognitive impairment (MCI) or dementia (for the controls)

2.5.5 Sample size calculation

To our knowledge, having explored the relevant literature, there is no clear consensus about the minimal clinically relevant effect size for such a study. However, we have found five similar studies (all the studies compare participants with DS to typically developing (TD) controls; 4 studies use age matching; 1 study uses age- and gender-matching) – details are shown in table 2.1, which focused on the P3b latency measure to compare people with DS to typically developing populations. These studies were selected based on how they: 1. Compare P3b latency between participants with DS and TD controls, and 2. Made the means and standard deviations of the P3b latencies, for both groups (DS, TD), available. The P3b measure has been selected as it has been most extensively studied in the AD and DS populations. From these five studies we found that the mean difference in P3b latency between groups across studies was 72ms and that the pooled standard deviation was 45ms, giving an "average" effect size of 1.6. The project also aims to investigate early markers of AD so we have considered previous studies that used the P3b latency measure to compare people with AD to typically developing populations. A recent meta-analysis of 40 studies which used the P3b latency measure to compare these groups found an average effect size of 1 (Howe, Bani-Fatemi, & De Luca, 2014, pg. 68, fig. 1). Powering a two-tailed t-test to detect a difference in means with the more conservative effect size of 1, a power of 95% and a significance level of 5% gave a sample size of 27 in each group (a total sample of n = 54). Therefore, assuming that a third of people are unlikely to tolerate the EEG procedure and produce usable data (Seidl et al., 1997), we aimed to recruit 36 people in each group (a total sample size of n = 72). To maintain an even age distribution, we ended up recruiting 43 people with DS and 39 age- and gender- matched controls, but only 36 of the participants with DS completed all of the electrophysiological measures.

Author	Sample	ERP Measures	DS P3 Latency (M, SD)	Controls P3 latency (M, SD)	Latency effect size (2 d.p.)	Key P3 Findings
Díaz & Zurron (1995)	12 children with DS (mean 14.16 yrs) 12 TD controls (mean 14.58 yrs)	SAEP, MAEP, LAEP: N1, P2, N2, **P3**	369.32 +/- 50.38	300.25 +/- 32.09	1.64	Relative to control participants, the N2 and P3 latencies were longer in DS.
Kakigi, et al. (1994)	47 adults with DS (18-48 yrs, M = 30.8 yrs, 26 males) 37 adults with AD (60-82 yrs, M = 68.5 yrs, 15 males) 43 younger TD controls (22-53 yrs, M = 30.8yrs, 17 males) 20 older TD adults (60-78yrs, M = 69.1yrs, 10 males)	**P300**	368.3 +/- 52.9	315.5 +/- 26.6	1.31	Only 24 adults with DS showed consistent ERPs, of which there was a delayed and frontal shift to the P300. This frontal shift was not present in the AD or TD (younger, older) participants.
Lalo, et al. (2005)	20 adults with DS (18-31 yrs, M = 24 yrs, 10 males) 20 TD adults (19-31 yrs, M = 25 yrs, 10 males)	N1, P2, N2a (MMN), N2b, **P300**	431 +/- 81	340 +/- 24	1.52	P3b was present in 55-65% of adults with DS, compared to 75-85% of controls, and was longer in latency.
Seidl et al. (1997)	10 children with DS (11-20 yrs, M = 15 yrs, 6 males) 10 age- and gender-matched TD controls (M = 15.1 yrs)	N1, P2, N2, **P3**	388.8 +/- 27.5	316.7 +/- 25.7	2.71	Participants with DS showed longer latencies for N1, P2, N2 and P3. The mean P3 amplitude at Cz was smaller in DS than TD, but not significantly. Between testing blocks the P3 amplitude decreased for TD participants but remained constant for DS participants
St. Clair & Blackwood (2013)	101 adults with DS (16-66 yrs) 88 TD controls (18-75 yrs)	N100, P200, **P300**	390 +/- 45	321 +/- 42	1.59	P300 waveforms were obtained from 90 adults with DS and 85 TD controls. For adults with DS, P300 latencies were significantly longer, and P300 amplitudes significantly smaller, than TD controls. P300 latencies increased with age for both groups, however the intercept for age-related change was 37yrs for DS and 53 yrs for TD.

Table 2.1 Previous studies which have compared P3b latencies between people with DS and typically developing controls, as a means of calculating the minimally clinical effect size, and therefore sample size, for the present study.

2.5.6 Sample composition

Completed all electrophysiological assessments at the *cross-sectional* phase:
36 x people with DS aged 20+ years (3 with DS-AD)
39 x age- and gender-matched typically developing (TD) controls

Completed repeat neuropsychological assessments at the *longitudinal* phase:
35 x people with DS

For the three participants with DS who also had a dementia diagnosis, the choice was made to retain them within the DS-group analyses. This decision was primarily made because AD pathology is an inevitable part of adult aging in DS (Mann, 2006). Therefore, adults with DS can be considered as at various stages of this pathological development. However, this PhD cannot meaningfully partition these stages of pathological development, and therefore the group cannot be meaningfully partitioned. Of course, a binary clinical judgement (AD, no AD) was made about the adults with DS. However, this binary judgement does not acknowledge those individuals who may be impaired by AD pathology but do not meet criteria for an AD diagnosis. Nevertheless, where appropriate, the contributions from the adults with DS who met clinical criteria for an AD diagnosis were highlighted on the graphical displays.

The between-groups (DS, TD) age- and gender-matching can be found in appendix Q.

2.6 Measures used with both age- and gender- matched control participants and participants with Down's Syndrome

2.6.1 Hearing

As the EEG paradigms involved the presentation of auditory stimuli hearing loss was screened for with the Siemens HearCheck Navigator, which has been validated as an appropriate tool (Fellizar-Lopez et al., 2011). The Siemens HearCheck Navigator sequentially delivers tones at two frequencies

(1000Hz, 3000Hz) and a range of decibels (20dB – 75dB). Participants who do not indicate hearing tones delivered at 1000Hz and 3000Hz at 55dB were excluded from the study and advised to seek a formal hearing test from their GP. This situation did not arise in the study.

2.6.2 Handedness

The Edinburgh Handedness Inventory (Oldfield, 1971) was used to assess participants' handedness.

2.6.3 Intelligence Quotient

The Kaufman Brief Intelligence Test, second ed. (KBIT; Kaufman & Kaufman, 2004) was used to approximate participants' (DS and controls) Intelligence Quotient (IQ). The KBIT II assesses verbal IQ with tests of verbal knowledge, and performance on riddles. The KBIT II assesses nonverbal IQ with performance on matrices. The combined performance forms an IQ composite, which is standardised by chronological age. KBIT II is used across all the studies in the Defeat Dementia in Down's Syndrome research stream.

2.7 Measures used with control participants only

2.7.1 Dementia screening

The age- and gender-matched typically developing controls were screened for dementia with the Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), and excluded from the study at the lower cut-off of 88. The ACE-R assessment and cut-off were employed to be able to exclude potential control participants with evidence of mild cognitive impairment (MCI) or dementia. The ACE-R was developed from the mini-mental state examination, and assesses subdomains which can be impaired in MCI and dementia: orientation, attention, memory, verbal fluency, language and visuo-spatial. No control participants were excluded from this study based on their ACE-R assessment. The ACE-R can be found in appendix R.

2.8 Measures used with participants with Down's Syndrome only

2.8.1 Blood tests

Blood samples were taken by a healthcare professional trained in phlebotomy at the Herchel Smith Building, Cambridge. Quantitative Fluorescent Polymerase Chain Reaction (QFPCR) analyses were performed on the extracted DNA to genetically confirm trisomy 21. The blood samples were also analysed to confirm APOE status. The blood samples were further analysed to identify pathology that could contribute to cognitive decline and behaviour change. The factors that may have potentially given a dementia presentation in the absence of AD: calcium deficiency, reduced liver function, reduced kidney function, hypo/hyperthyroidism and vitamin B12 deficiency. A full blood count and creatinine levels were also taken. However, venepuncture was very difficult with many of the participants with DS, so only 15 participants had their blood taken for karyotyping and APOE status analysis. Due to the small number of samples, blood results were not made use of in this study. To adhere with ethical protocols, any abnormal blood results were reported to the participants' GP.

2.8.2 Neuropsychological assessments

The study followed the neuropsychological testing schedule set out in the amyloid imaging study (11/EE/0348), in the interests of consistency and comparability between the projects. The tests were developed, or adapted, to be appropriate for people with intellectual disabilities and cognitive decline associated with dementia. The full battery of neuropsychological tests is as follows:

- The Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities: CAMDEX-DS (Ball et al., 2006; Roth, Tym, & Mountjoy, 1986), which includes an informant interview and cognitive assessment (CAMCOG-DS).

- The Executive Function test battery for people with DS (EFDS) (Ball et al., 2008).
- The Arizona cognitive test battery (Edgin et al., 2010).
- The Severe Impairment Battery (SIB) (Saxton, McGonigle, & Swihart, 1993).

Only tests directly relevant to the aims and hypotheses of this thesis, focusing on cognitive decline and executive dysfunction, were analysed and are described in greater detail below. The relevant measures are: the CAMDEX-DS, including CAMCOG-DS, and the battery of EFDS tests, which can be found in appendices S-V.

2.8.3 The CAMDEX-DS– (Ball et al., 2006)

The CAMDEX-DS (Ball et al., 2006) was developed to be informative about the development of dementia in people with intellectual disability. The tool includes a cognitive assessment component (CAMCOG-DS) and an informant interview (CAMDEX-DS).

The CAMCOG-DS assesses participants on seven functional domains affected by the presence of AD: orientation, language, memory, attention, praxis, abstraction, and perception. The total available score from subscales is 109. The assessment is designed to avoid floor effects, and is based on well-established dementia assessments for the general population (Mini-mental status examination) and people with severe ID (SIB).

The CAMDEX – DS informant interview (Ball et al., 2006; Roth, Tym, & Mountjoy, 1986) was used to indicate cognitive decline and diagnose dementia in DS. A dementia diagnosis from the CAMDEX – DS is a clinical decision based on parent or carer reports of the participant's: best level of functioning, cognitive and functional decline mental, and physical health (Ball et al., 2006). The interviewee is selected on the basis of having had regular contact with the participant for at least 6 months prior to the assessment. In this study the dementia diagnosis of a participant with DS was made by an experienced psychiatrist reviewing, blind to the age, gender and previous diagnostic status of the participant, the researcher's CAMDEX – DS informant interview with the parent or carer. Three participants were diagnosed as having dementia at the cross-sectional phase with this method. No participants transitioned to a dementia diagnosis, as assessed with the CAMDEX – DS, at the longitudinal phase.

2.8.4 *The Executive Function test battery for people with DS* – (Ball et al., 2008)

The Executive Function test battery drew from previous tests of executive function originally developed for the general population. The tests were further developed or adapted by Ball et al., (2008), to be appropriate for people with intellectual disabilities. The total EFDS score is 51. The subtests that make up this score are described below.

The cats and dogs task

The cats and dogs task is a simplified version of the day-night stroop task (Gerstadt, Hong, & Diamond, 1994). The task primarily tests response inhibition. In the task, participants are first instructed to sequentially identify the cats and dogs along a strip of paper. Then the rule changes, so every time the participant sees a cat they should say "dog", and every time they see a dog they should say "cat". Participants are timed in the task. The maximum score is 16, from which the number of errors made is subtracted to give the participants' personal score.

The Tower of London task

The Tower of London Task was standardised by Krikorian, Bartok, & Gay, (1994), as an informative test of planning and working memory. As part of the EFDS battery development, the task demands were reduced from twelve to four puzzles (Ball et al., 2008). In the task, both the researcher and the participant have a block. On each block are three pegs, of reducing length, and three beads (red, blue and green). The participant is tasked with moving one bead at a time so their block looks like the researcher's. The participant must do this within a set number of moves (two, three, four or five), which correspond to difficulty levels. The participant is given two practice opportunities at the beginning of the session after which scoring begins. Participants have a maximum of three attempts at each level. Full marks (three points) are awarded for participants who complete the level on the first attempt, two points for completion on the second attempt, and one point for completion on the third attempt. If the participant fails on the third attempt and does not receive points for the level then the task ended. The maximum score on the task is 12 points.

The Weigl Sorting task

The task was developed by Weigl, (1941), then further developed by Strauss and Lewin (1982), to assess extra dimensional set shifting. For the EFDS battery, Ball et al. (2008) adopted a positive scoring system. The researcher begins by placing the cards on the table and asking the participant to sort them so “the ones that belong together are in a pile together”. The participant should then sort the cards into piles of shared colour or shape. If the participant fails the initial sort then a score of 0 is given for the task. For participants who achieve the initial sort, the researcher asks them to sort the cards so “they belong together in a different way”. If the participant achieves the spontaneous set shift at this level then they are awarded five points. The more instructions a participant needs to achieve the spontaneous set shift, the fewer points they receive. If the researcher has to explicitly tell the participant to re-sort the cards by colour/shape (as appropriate), then the minimum of one point is awarded.

The spatial reversal task

This task was originally developed by McEvoy, Rogers, & Pennington (1993) to assess set shifting within the spatial domain. The task also assesses response inhibition. The task is premised on the participant finding the coin from a forced choice of two boxes. The participant can only lift one box on each trial to find the coin. The coin remains under one box until the participant has found it there, four consecutive times. At this point the coin moves under the other box, and the participant must learn the new rule. The task is made difficult by placing a screen between the participant and the boxes. The screen is put up between each trial and the researcher pretends to move the boxes around, behind the screen. If this set shift stage is not attempted or if the participant fails to learn the first rule after ten attempts, then no points are awarded. The maximum score is seven points, accrued at the set shift phase.

The scrambled boxes task

The testing procedure was from Griffith, Pennington, Wehner, & Rogers, (1999), and slightly modified by Ball et al., (2008) to be a test of working memory and response inhibition for the EFDS battery. The task requires participants to find three coins, from three separate boxes, labelled with different shapes. The participant watches the researcher hide the coins in the boxes. The participant then points to a box where they think a coin is. The researcher then opens the selected box to tip out a coin or indicate that it is empty. The researcher then replaces the lid of the box and the search for coins continues. In the first round the three boxes are stationary between searches. In the second round the three boxes are scrambled between searches. If the participant passes the three-box scrambled condition then the test moves to a six-box stationary condition. Again the participant watches the researcher put coins in three of the six boxes. If this stage is passed then participants move to the final rotation, whereby the boxes are scrambled between searches. Only the scrambled conditions are scored. Participants can receive a maximum of four points for the three-box scrambled condition, and seven points for the six-box scrambled condition. Whenever the participant searches in a box where there is no coin, one point is subtracted from their total score.

2.9 *Testing schedule*

2.9.1 *Testing schedule table*

The testing schedules, order and timings, for the participant groups (DS, TD) are shown in table 2.2.

Task category	Task	Participant group		Total time required (minutes)
		DS	TD	
Day 1. Home (or other convenient location for participant) visit by researcher				
Pre-engagement checks:	Seeking consent	✓	✓	15
	Siemens HearCheck Screener	✓	✓	5
	Measure head circumference with tape measure to determine EEG cap size needed	✓	✓	1
	Edinburgh Handedness Inventory	✓	✓	5
Cognitive measures: *Note.* some measures may be administered over two home visits or during the Cambridge visit instead to lessen demands on participants	CAMCOG-DS	✓	×	30
	KBIT II	✓	✓	20
	SIB	✓	×	15
	EFDS	✓	×	30
	Oliver Object Memory Test and Test for Sentences	✓	×	5
	Selected tests from ACTB (including CANTAB)	✓	×	60
	ACE-R	×	✓	15
Total testing time per group for day 1 (minutes) :		186	61	
Day 2: Cambridge visit by participant to the EEG Lab, Herchel Smith Building				
Diagnostic measure:	Venepuncture for a 10ml blood sample, taken by a research nurse, for subsequent genetic testing to confirm DS diagnosis	✓	×	10
Electrophysiological measures:	Fit the EGI's HydroCel Geodesic Sensor Net 130 (EEG cap)	✓	✓	5
	Gently push aside the hair under each electrode and deposit a small amount of gel, with a plastic syringe	✓	✓	30
	Press and click a digi-pen on each electrode so their positions are digitised onto the Brainstorm computer programme	✓	✓	10
	Record resting state EEG data onto the NetStation computer programme (5 minutes eyes open, 5 minutes eyes closed)	✓	✓	10

	Use MATLAB to play tones, paired-clicks, and record onto NetStation time-locked responses: P50 suppression	✓	✓	20
	Use MATLAB to play tones, within the global-local paradigm, and record onto NetStation time-locked responses: MMN, P300 (P3a, P3b)	✓	✓	40
Total testing time per group for day 2 (minutes) :		125	115	
Day 3: Repeat home (or other convenient location for participant) visit by researcher. This visit is conducted approximately 12 months later than "Day 1"				
Pre-engagement checks :	Seeking consent	✓	×	15
Cognitive measures:	CAMCOG -DS	✓	×	30
Total testing time per group for day 3 (minutes)		45	0	
Total testing time per group for the study (minutes) (day 1 + day 2 + day 3):		356	176	

Table 2.2. A schematic of the testing procedure for each group. DS = Down's Syndrome, TD = age- and gender- matched typically developing controls. Please note that multiple breaks were taken, as appropriate for each participant's fatigue level, which altered the final testing time.

2.9.2 The cross-sectional testing schedule

For participants with DS:

- 2-3 home visits, made by the researcher: 2-3 hours each of neuropsychological testing, including breaks. The first session also included the consent procedure. The parent or carer also had a 30 minutes – 1 hour informant interview on one of these visits, or by telephone.
- 1 Cambridge visit, made by the participant and the parent or carer: 2.5 hours average of electrophysiological testing, including breaks.

For age- and gender-matched controls:

- 1 Cambridge visit, made by the participant: 3 hours of testing which included the consent procedure, neuropsychological and electrophysiological testing.

2.9.3 The longitudinal testing schedule

For participants with DS:

- 1 home visit, made by the researcher: 45 minutes of consent procedure and neuropsychological testing with the participant, and 30 minutes – 1 hour of informant interview with the parent, or carer.

2.10 Map of home visits

All of the locations that the researcher visited for the cross-sectional and longitudinal home visits are shown in figure 2.2.

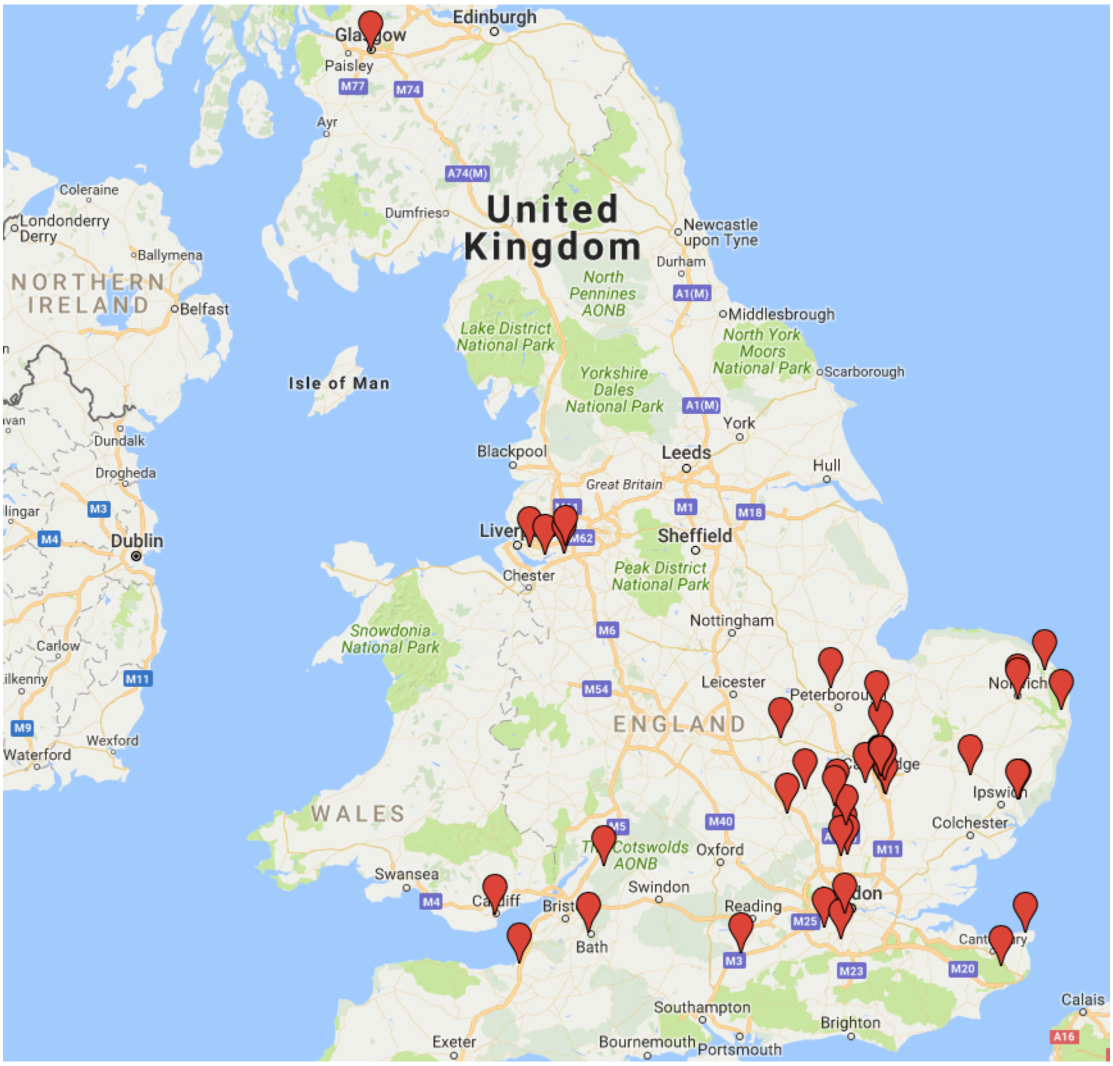

Figure 2.2. Map of home visits made by the researcher.

2.11 Home visit safety

A thorough risk assessment was conducted to assess any safety risks for visiting participants with DS. Researchers adhered to the ‘buddy system’, whereby a colleague was aware of the visit location and the researcher contacted them when they arrived and left. The participants were always visited with ‘the person who knows them best’, and in their home environment so they were as comfortable and relaxed as possible.

The next section is concerned with electroencephalography (EEG), more specifically the global-local paradigm, which gleans the event related potentials (ERPs): mismatch negativity (MMN), P300 (P3a and P3b).

2.12 Electroencephalography

An electroencephalogram (EEG) is a recording of bio-electrical activity generated by cortical neurons. The raw recording is a coarse measure of neural activity (Luck, 2005). Event-related potentials (ERPs) are extracted from EEG recordings as averaged, time-locked, specific neural responses to specific stimuli (Luck, 2005). ERPs are characterised by latency and amplitude features. The latencies of ERPs index the time taken to process stimuli whereas their amplitudes reflect cognitive resource allocation for stimuli processing (Duncan et al., 2009).

The neural origins of EEG signals begin with action potentials. Action potentials are the travel of discrete voltage from the soma (cell body) to the pre-synaptic terminals of the axon, stimulating the release of neurotransmitters into the synaptic cleft (Luck, 2005). The released neurotransmitters then bind to receptors on the post-synaptic terminal, which stimulates the ion channels to open or close, resulting in a graded change in post-synaptic potential (Luck, 2005). Excitatory postsynaptic potentials (PSP) promote the transportation of positively charged ions (Na^+) into the cell, typically at the apical dendrites site, a ‘sink’ (Lopes da Silva, 2004). Inhibitory PSPs promote the transportation of negatively charged ions (Cl^-) into the cell, typically at the soma, a ‘source’ (Lopes da Silva, 2004). This generates a potential difference, or ‘dipole’, between the apical dendrites and soma. The currents flow, intracellularly, from the apical dendrites to the soma. The extracellular volume currents complete the loop. The loop results in the characteristic ‘rise and fall’ fluctuations see on EEG recordings. The figure below (figure 2.3) from Lopes da Silva (2004) visualises the neural origins of EEG recordings.

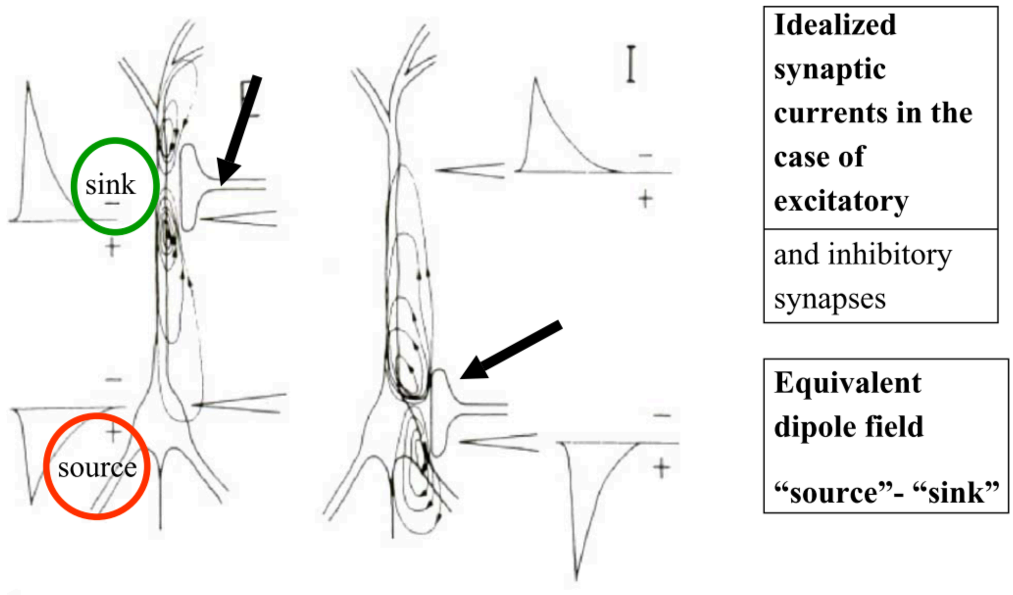

Figure 2.3. from Lopes da Silva (2004) which visualises the neural origins of EEG.

Only the summation of at least 50000 PSPs is detectable by electrodes at the scalp, and therefore recordable as EEG. In order for the dipoles of PSPs to summate, rather than cancel one another, they must not only be proximal but share orientation and stimulation (excitatory/inhibitory) (Luck, 2005). The recordings are typically made from pyramidal cells because of their perpendicular alignment (Luck, 2005). However, waveform polarity (positive or negative) is determined by the location and orientation of the cortical, synaptic activity (Burgess & Collura, 1993). A visualisation of polarity can be found in figure 2.4.

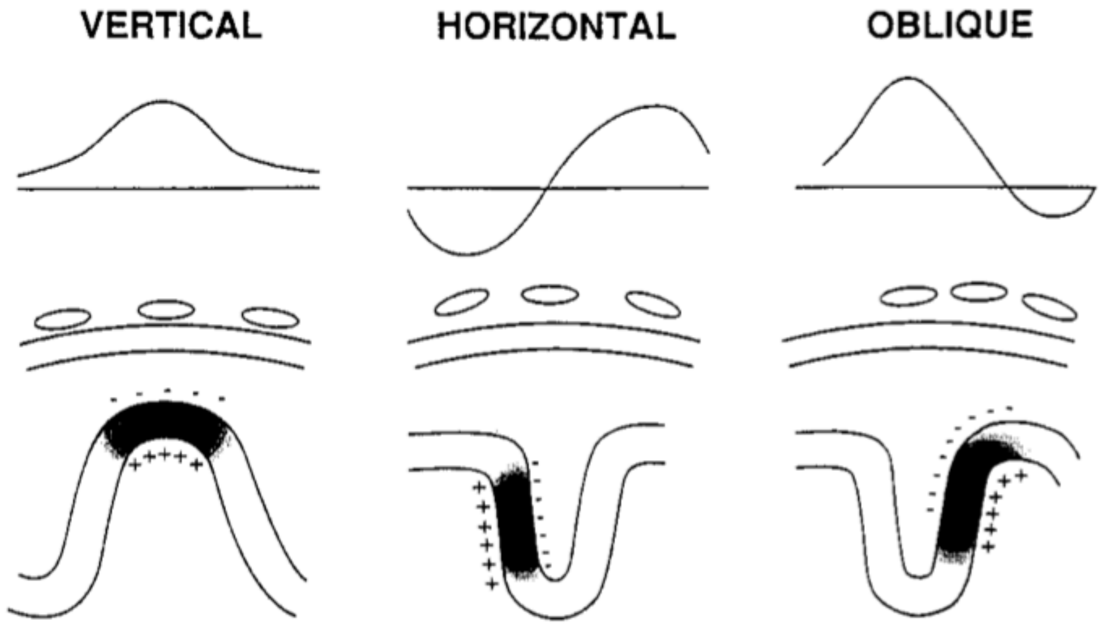

Figure 2.4. A visualisation of EEG polarity from Burgess and Collura (1993).

Synchronous firing as a time-locked, processing response to specific stimuli is termed event related potentials (ERPs) (Peterson, Schroeder, & Arezzo, 1995). ERPs are extracted as averaged waveforms from EEG recordings (Luck, 2005). ERPs have two categories: 1. Exogenous: an early (within 100 ms) sensory response that is driven by the properties of the stimulus, and 2. Endogenous: a later (post 100 ms) cognitive response of evaluating and processing the stimulus (Sur & Sinha, 2009). The present study is focused on endogenous components: mismatch negativity (MMN) and P300 (P3a, P3b).

MMN is a negative waveform generated from the difference in response to standard and 'mismatched' tones, in the absence of conscious attention (Hinkley et al., 2010). MMN reflects automatic sensory memory processes involved in pre-attentive cognition. A visualisation of how MMN is generated is shown in figure 2.5.

P300 is a positive waveform of two components: P3a and P3b. P3a is the earlier component, known as the 'novelty response' to a distracting, rare stimulus (Friedman et al., 2001). Whereas P3b is the later component that requires active, attentive processing to target stimuli (Polich, 2007). A visualisation of the two components is available in figure 2.6.

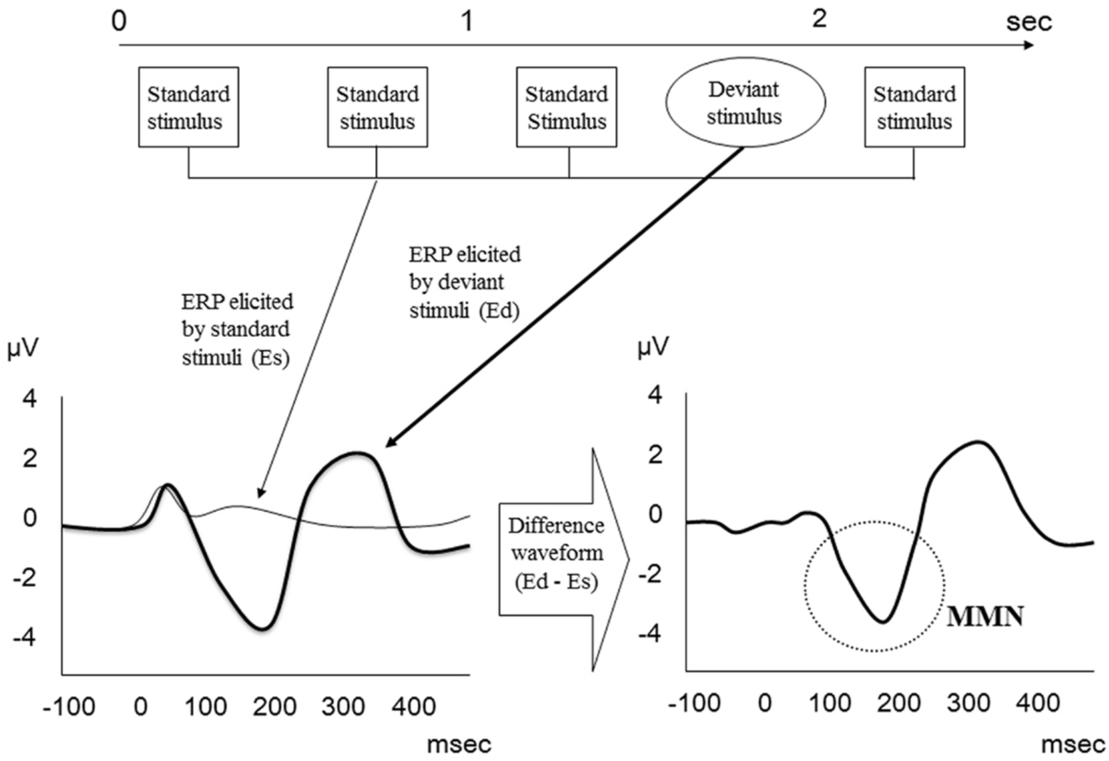

Figure 2.5. The generation of an MMN waveform, adapted from Hinkley et al. (2010).

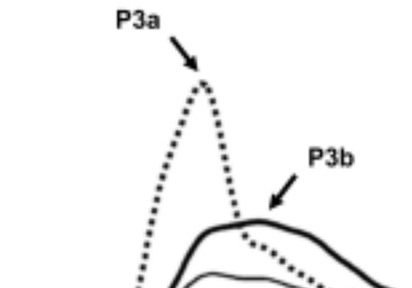

Figure 2.6. P3a and P3b waveforms, adapted from Polich (2007).

EEG records bio-electrical activity generated at the cellular level, essentially, instantaneously at the scalp (Luck, 2005). The technique has exquisite temporal accuracy, however the source of the signal is smeared as it spreads through the conductive medium of the scalp, limiting spatial resolution. MEG records the magnetic fields generated from the electrical currents and provides improved spatial resolution but at the cost of only being able to record radial dipoles, whereas EEG can record from both tangential and radial dipoles.

2.13 Global Field Power

The EEG analyses in this thesis are predominantly focused on Global Field Power (GFP). Lehman and Skrandies first described the GFP computation in 1980, as a spatial standard deviation. The premise of GFP is that more field lines indicate that more synchronous neuronal activation is being recorded, and therefore more information is gained (Skrandies, 1990). GFP computes field activity, at each time point and electrode, as a mean of all the absolute potential differences (Lehmann & Skrandies, 1980). The result corresponds to the spatial standard deviation (Lehmann & Skrandies, 1980). GFP is plotted as a function of time, and the time at which the GFP reaches it's maximum (largest deviation), can indicate the latencies of ERPs (Skrandies, 1990). The advantages of GFP include that as a reference- and polarity-independent technique, electrophysiological data from all the recording electrodes are evaluated to determine the power of deviations (i.e. ERPs), within a given time frame (Lehmann & Skrandies, 1980). The results are also less ambiguous than typical waveshape analyses (Skrandies, 1990).

2.14 Electroencephalographic assessments

All electrophysiological assessments were conducted in the EEG Lab at the Herchel Smith Building, Cambridge. A high-density array EEG net of 129-channels (HydroCel Geodesic Sensor Net by Electrical Geodesics Inc., Eugene, Oregon) was used. To ensure good conductance of the electrodes, the hair directly underneath the electrodes was gently pushed aside and a small amount of conducting gel (Spectra 360) deposited on the exposed scalp, with a plastic syringe. Then, the location of each electrode on the scalp was digitsed onto the Brainstorm computer programme by sequentially clicking a digi-pen to each electrode. Participants were then seated in an electronically shielded room and the EEG net they were wearing plugged into the Net Amps 300 amplifier (Electrical Geodesics Inc.) so continuous EEG data could be collected and recorded onto the NetStation software package. The researcher watched participants during testing via a live video feed. The recording parameters were: <100KOhms impedance, 1000Hz sampling rate for resting-state EEG collection, 500 Hz sampling rate for ERP collection, and referenced to the vertex. The electrophysiological data was recorded for resting-state EEG. A paired clicks paradigm was also used to generate a P50 suppression effect. Finally, the 'global-local' task, which is an auditory oddball paradigm, was used to generate MMN, P3a and P3b. The resting-state EEG data was ten minutes of EEG recording, five minutes eyes open with a fixation cross and five minutes eyes closed, from participants sitting, relaxed and comfortable, in a dimly-lit room. The ERPs (P50 suppression, MMN, P3a, P3b) were elicited by auditory stimuli (tones). The auditory stimuli were presented to participants: using Psychtoolbox version 3 (Brainard, 1997) running in MATLAB; at a comfortable volume as judged by participants; binaurally; through Etymotics ER-3A earphones. During the P50 suppression task participants watched, without sound, the first 20 minutes of the season 1, 'Spring' episode of 'Frozen Planet'. The focus of this thesis is on the 'global-local', auditory oddball paradigm which elicited: MMN, P3a and P3b ERPs.

The global-local paradigm was selected because the multi-level design generates three ERPs (MMN, P3a, P3b) within a predictive coding framework, which makes an interesting addition to the analyses and conclusions. Furthermore, MMN and P3b have been tested in separate AD, DS and aging populations previously. These factors will be explored together in the present study. MMN has been most successfully linked with frontotemporal dementia (Hughes & Rowe, 2013), which is of interest in the present study as frontal-type symptoms are some of the earliest indicators of AD in DS. P3b is the most studied ERP in the AD literature but, to our knowledge, P3a has been little studied, which adds an exploratory component to the study.

2.15 Global local paradigm

The global-local paradigm was originally developed by Bekinschtein et al., (2009) to clearly delineate MMN, P300 components within one odd-ball paradigm. The paradigm has two levels of deviation: 1. Global – between trial variance: when a different group of sounds elicit a P3b component, when explicit attention is paid to the difference; 2. Local – within trial variance: when different individual sounds elicit MMN and P3a components. The local effect is present in the absence of explicit attention.

At the beginning of testing, for the present study, participants were informed that they were about to hear groups of sounds. Participants were asked to listen carefully to the groups of sounds because at the end of each block they would be asked: "can you tell me what group of sounds you heard a lot?" and "can you tell me what group of sounds you heard sometimes?". Participants' answers were recorded at the end of each block. The purpose of the questioning was to maintain participants' attention on the groups of sounds (global effect). At the end of each block, participants were also asked about their arousal levels on a scale of 1-10 (1 – Asleep to 10 – Fully awake), and attentiveness (1 – Mind wandering/unattentive to 10 – Fully attentive to stimuli). Participants took a break between each block at a length of their choosing. A total of 8 experimental blocks were presented, with total testing time, including breaks and questioning, taking an average of 40 minutes.

Each participant was played tones at a volume that they indicated as audible and comfortable. The tones were mixtures of three sinusoids of either type: A (500, 1000, and 2000 Hz), or B (350, 700, and 1400 Hz). These mixtures are identical to those used in the original development (Bekinschtein et al., 2009). Each tone lasted 50ms and was presented in a five-tone group, with 100ms intervals. The tone sequences consisted of either five identical tones (AAAAA or BBBBB), or four identical tones then a different tone (AAAAB or BBBBA). The tone sequences were presented either entirely monaurally, to the left or right ear, or predominantly monoaurally with an interaural, opposite ear, final tone.

The grouping of the tones into sequences determined their status as: local standards, local deviants, global standards, global deviants or interaural deviants. The 'local' sequences focus on the individual tones. The 'local standard' is when the five tones in the sequence are identical (AAAAA or BBBBB). The 'local deviant' is when the fifth tone in the sequence differs in type (AAAAB or BBBBA), and/or laterality, 'interaural deviant' (AAAA*A*, BBBB*B*, AAAA*B*, and BBBB*A*). The 'global' sequences are concerned with comparing tones at a group (sequence) level. The 'global standard' is the repetitive five-tone sequence; the 'standard' is tied to the repetition with the block rather than the tone type (A or B). The 'global standard' is presented 100 times within a block, making up approximately 71.5% of the testing presentations. The 'global deviant' is the five-tone sequence, which differs from the 'standard' in the block. The 'global deviant' sequence is psedorandomly presented between 19 and 21 times in a block (14.25% of presentations) in a monoaural form, and a further 19-21 times (14.25%), in an interaural form. The pseudorandomisaton procedure consisted of deviant sequences being interspersed with two to five standard sequences, and two to three standards preceding the next 80% of deviants. The full list of global deviants and global standards is listed in table 2.3, and a schematic of presentations is available in figure 2.7.

There were eight experimental blocks, each containing approximately 160 sequences (groups of sounds). Each block was counterbalanced by the dominant tone type (A or B) and laterality of monoaural tone delivery (left or right). The 'global standard' was established at the beginning of the testing phase with 3s of silence followed by 20 presentations of the monoaural sequence. The testing phase of the block contained 138-142 sequences. The sequences were separated by randomly sampled periods of silence, which last between 700ms and 1000ms. The eight experimental blocks were structured into 'X' and 'Y' types, as in table 2.3, allowing for across-block orthogonal contrasts. For example, a global standard monoaural sequence of AAAAA, in block X, would also be a local standard. Conversely, against a global standard monoaural sequence of AAAAB, the AAAAA sequence could be considered a global deviant. Due to the predominance of monoaural delivery, lateral, interaural tone delivery was always locally and globally deviant. The analyses were focused on contrasts, which included an inter-aural deviant. The block presentation is also pseudorandomised so that the initial presentation is always an X block, and only two blocks of the same type (X or Y) can be presented consecutively. The block design is laid out more clearly in table 2.3.

Laterality	**Tone type**	**Block type**	**Global standard**	**Global deviant**	**Interaural deviant**
Left	A	X	AAAAA	AAAAB	AAAA*A*
Left	B	X	BBBBB	BBBBA	BBBB*B*
Left	A	Y	AAAAB	AAAAA	AAAA*B*
Left	B	Y	BBBBA	BBBBB	BBBB*A*
Right	A	X	AAAAA	AAAAB	AAAA*A*
Right	B	X	BBBBB	BBBBA	BBBB*B*
Right	A	Y	AAAAB	AAAAA	AAAA*B*
Right	B	Y	BBBBA	BBBBB	BBBB*A*

Table 2.3. The eight experimental blocks presented as auditory stimuli in the global-local paradigm. The blocks are counterbalanced for: laterality, tone type, and deviance. The italicised letter indicates the interaural deviant.
The table is adapted from (Chennu, Noreika, et al., 2013).

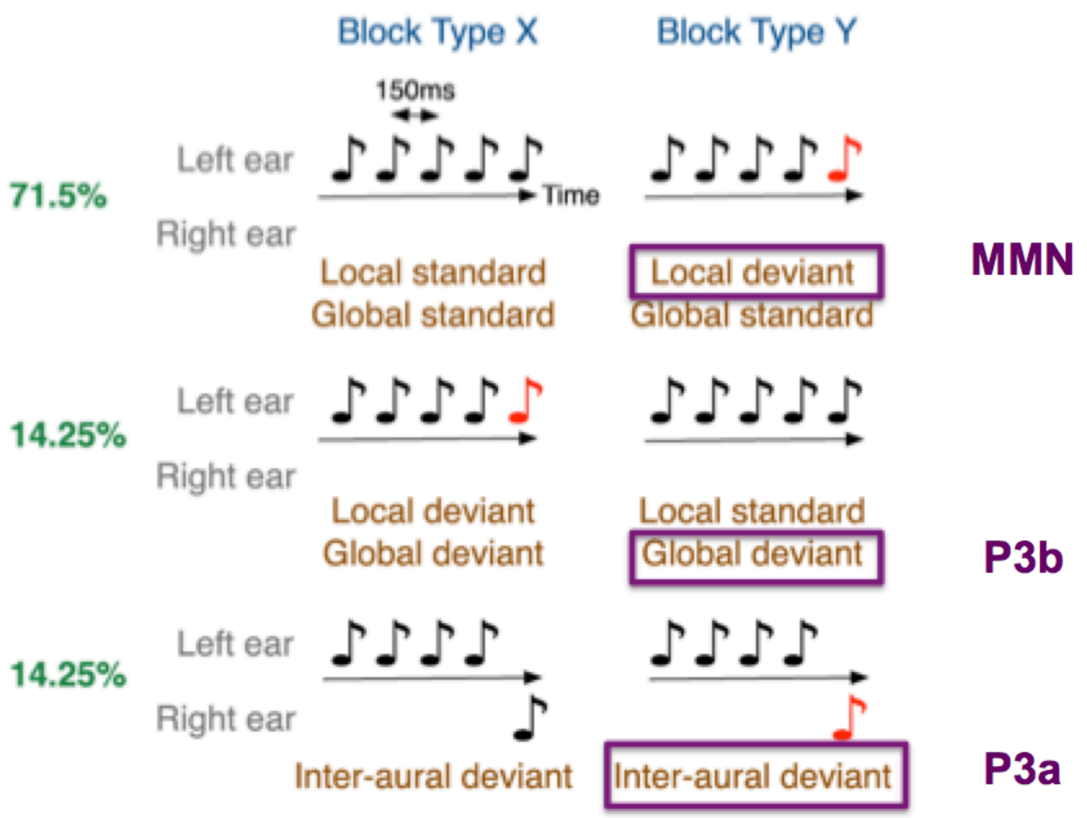

Figure 2.7. A schematic of the experimental design, adapted from Chennu, Noreika et al., (2013). One sequence is composed of five tones, visualised as notes in the schematic. The black notes in a sequence are the same A or B tone; the red notes are the comparatively different A or B tone. For the X blocks, the standard sequences were monoaural repetitions of the same tone type, with deviation in tone type (A or B) or laterality (left or right). Conversely, for Y blocks, the fifth tone of the standard sequences differed in type. This differing context (X or Y blocks) allows the same stimuli sequence to elicit a different ERP (MMN, P3a, P3b).

2.16 Pre-processing

The sequence below is of the custom MATLAB scripts, with Statistical Parametric Mapping (SPM) utility, used to pre-process the raw EEG data gathered with the global-local paradigm. The pre-processing pipeline was originally developed by Dr Tristan Bekinschtein and Dr Srivas Chennu, and then adapted for the present study by Dr Srivas Chennu. Miss Sally Jennings conducted the pre- and post-processing analyses. The purpose of each step is described.

During pre-processing, the researcher was blinded to the participant's identify but not group (DS, controls).

Step 1. Data import – the data is imported and converted to a MATLAB-SPM appropriate file type so analyses can continue. During this step the data are also down-sampled from 500Hz to 250Hz, to make the files a more manageable size. The channel locations and head shape from GSN-HydroCel-128 is also loaded. A low pass filter of 25Hz and high pass filter of 0.5Hz is also applied. This version of the file is then saved, with an appropriate ending to be picked up by the next script. This saving method is true of each preprocessing step.

Step 2. Delete channels – channels on the neck, cheeks and forehead, which by virtue of their location would hold more noise than signal, were removed from further analyses to remove unnecessary noise from the data. The channels excluded were:

1,8,14,17,21,25,32,38,43,44,48,49,56,57,63,64,68,69,73,74,81,82,88,89,94,95,99,100,107,113,114,119,120,121,125,126,127, and 128.

The following analyses were restricted to the remaining 90 channels. A visualization of the channels can be found in figure 2.8.

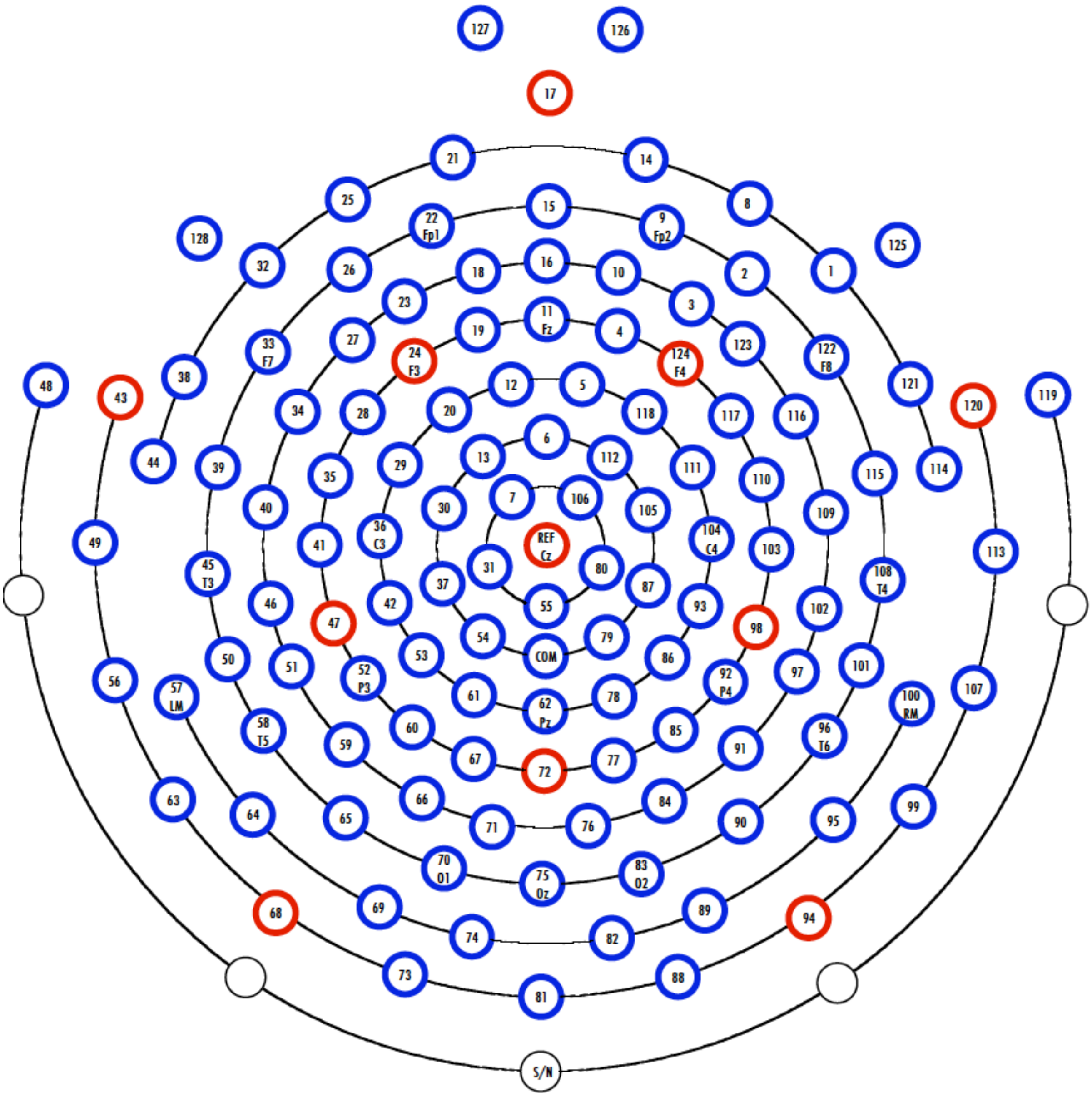

Figure 2.8. The HydroCel Geodesic Sensor Net 128 channel map, taken from the Electrical Geodesic manual.

Step 3. Epoch data – the data was sectioned within windows -200 to 700ms, relative to the fith tone, to create epochs of interest. The ERPs were calculated 50-650ms post stimulus. Epochs were baseline corrected between -200 – 0ms preceding the onset of the fith tone.

Step 4. Mark bad trials and channels – bad trials and channels were visually identified and marked. The channel variance threshold (T1) was set at 40000; The trial variance threshold (T2) was set at 2000. The purpose was to remove only the worst trials as the rest could predominantly be corrected for with Independent Component Analysis (ICA). Please find an example of the thresholds below, in figure 2.9.

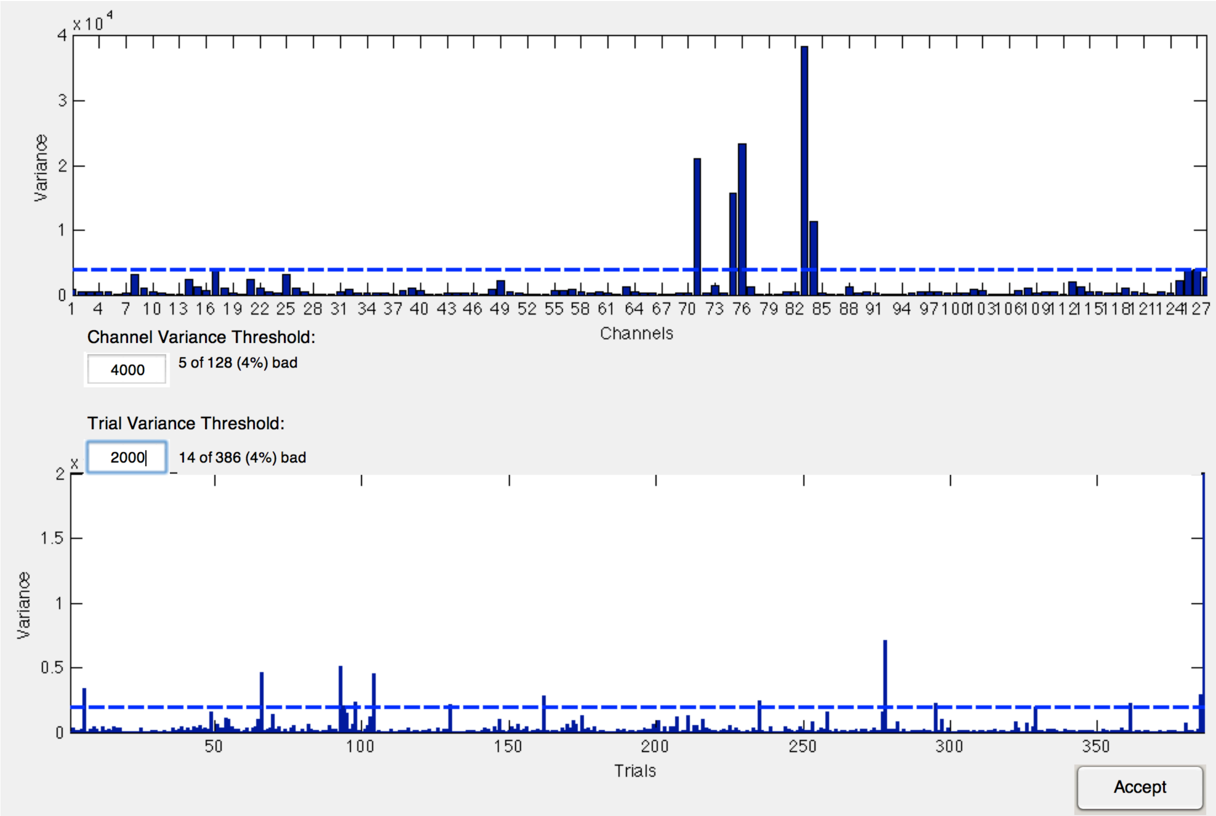

Figure 2.9. The blue dashed line indicates the threshold. Channels and trials whose variance exceeds the threshold are marked for removal.

Step 5. Reject artifacts - bad trials and channels, which were highlighted at the 'mark bad' stage were removed. Rejected channels were interpolated with spherical spline interpolation.

Step 6. Compute ICA – the EEGLAB toolbox was employed to run Independent Component Analysis (ICA) on the data.

Step 7. Mark ICA – used to bring scalp maps and time course plots of the ICA components. The technique was purposed to remove well-defined artifacts such as muscle movement, eye blinks and roving eye movements, without losing an epoch of data. Please find below, in figure 2.10, an example IC.

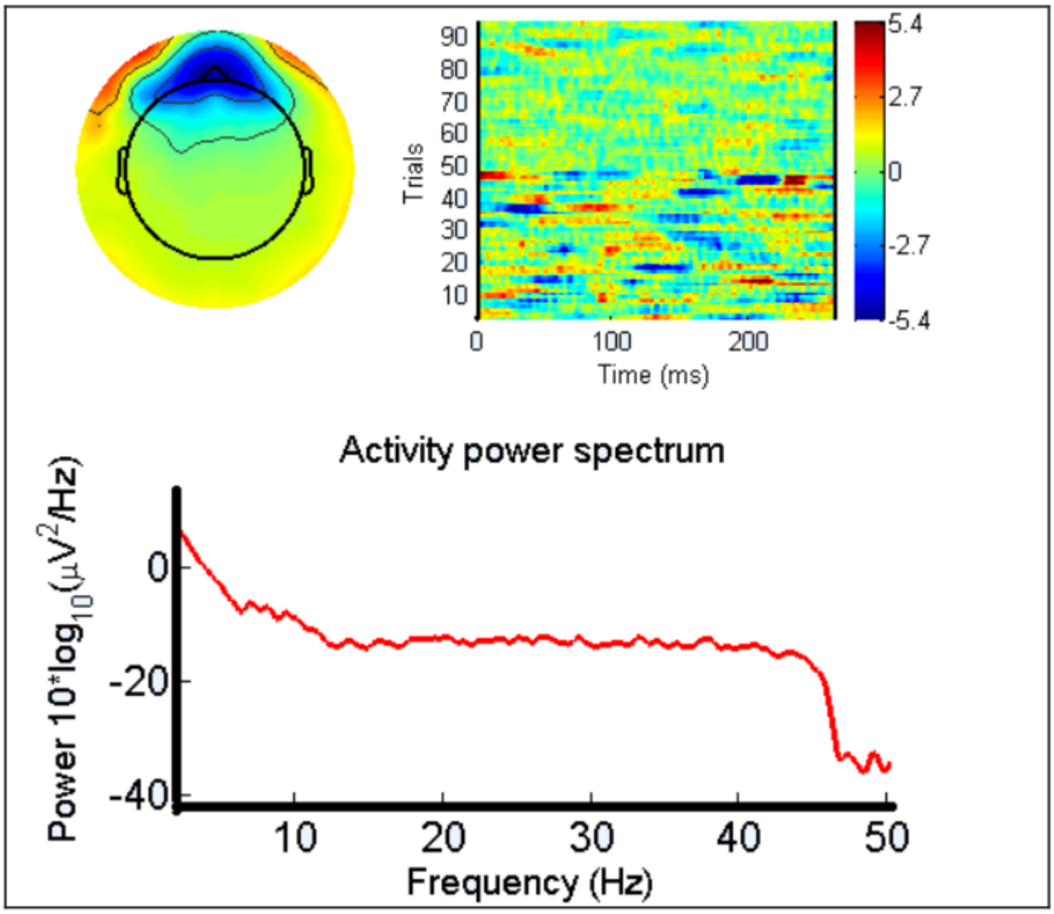

Figure 2.10. The figure shows a characteristic slow-eye blink IC for removal. The nature of the IC is revealed in the isolated ocular location of the activity, shown on the scalp map (top left).

Step 8. Reject ICA – to reject independent components, which had been marked for removal at the 'mark ICA' stage

Step 9. Mark bad trials and channels – to identify any remaining bad channels/trials after ICA. T1 corresponds to channels and was set at 500; T2 corresponds to trials variance and was set at 250. The same threshold system is used as before.

Step 10. Reject artifacts - bad trials and channels that were highlighted at the 'mark bad' stage were removed. Rejected channels were interpolated with spherical spline interpolation.

Step 11. Re-reference – the data was re-referenced to the mastoid sites ('E57' 'E100').

Step 12. Calculate ERPs – condition-wise ERPs were calculated. The conditions were: ld = local deviant, ls = local standard, gd = global deviant, gs = global standard, ad = inter-aural deviant. The condition list pairs for each ERP are set up as: MMN – (ld,ls), (ad,ls); P3a – (ad,ls), (ad,gs); P3b – (gd,gs), (ad,gs).

Step 13. Grand average – average ERPs by participant and group (DS, controls).

Step 14. Generate images – sensor/source images were generated for SPM applicable statistics, as SPM only works with images.

Step 15. SPM batch – to build an SPM general linear model (GLM) on the sensor/source images. This was set up in terms of the contrast of interest. For example, to set up a between groups (DS, controls) comparison, as seen in Chapter 3, the following was used:
spmbatch({'downs','controls'},'EEG')

Step 16. Plot contrasts – used to plot the contrasts of interest: MMN – (ld,ls), (ad,ls); P3a – (ad,ls), (ad,gs); P3b – (gd,gs), (ad,gs).

Step 17. Print cluster – used to load contrasts and identify clusters of interest, the script is detailed in the appendix W.

Step 18. Plot cluster – used to image the spatio-temporal clusters of interest. An example of the controls group MMN is as follows:
plotcluster('controls',{'ad','ls'},'mmn','EEG','statwin',[50 650],'dir','neg')

The plot cluster function gives the output seen in figure 2.11.

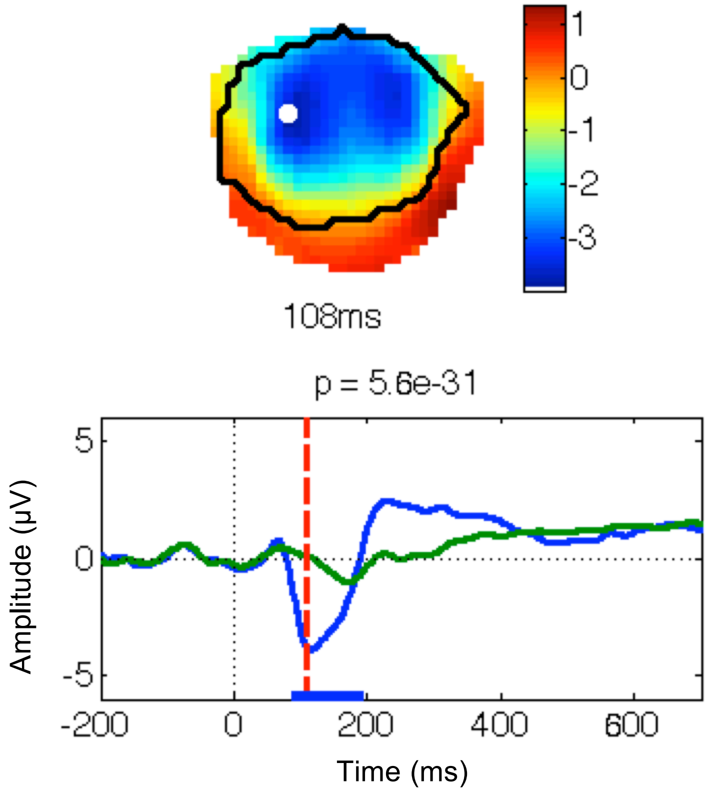

Figure 2.11. Age- and gender-matched controls MMN*.* The black outline identifies the significant cluster. Blue indicates negative activity whereas red indicates positive. The white electrode is the electrode in which the difference between the deviant and standard is maximal, and is mapped out below the scalp map. The green line indicates the response to standard tones. The blue line indicates the response to deviant tones. The *p* value is the significance of the difference between the tones, and the time in ms indicates the time course being mapped out.

Step 19. Plot ERPs – used to plot the ERPs. Masking is used: MMN: 100-200, earlier P300: 200-400, later P300: 400-650. This is a small volume correction which, using the 50-650 range, focuses in the analysis on the a-priori analysis windows of interest so they are not masked by the other ERPs and variance. The choice of time-windows is 1. Informed by the literature, and 2. Confirmed statistically with spatio-temporal cluster analyses, and visually at the 'plot cluster' stage. The literature justification for the time-windows is described in the chapter 3, section 3.3. The spatio-temporal cluster analyses are described in chapter 3, section 3.5.2. The output from the ‘plot ERP’ stage is shown in figure 2.12. This technique is predominantly used in chapter 5.

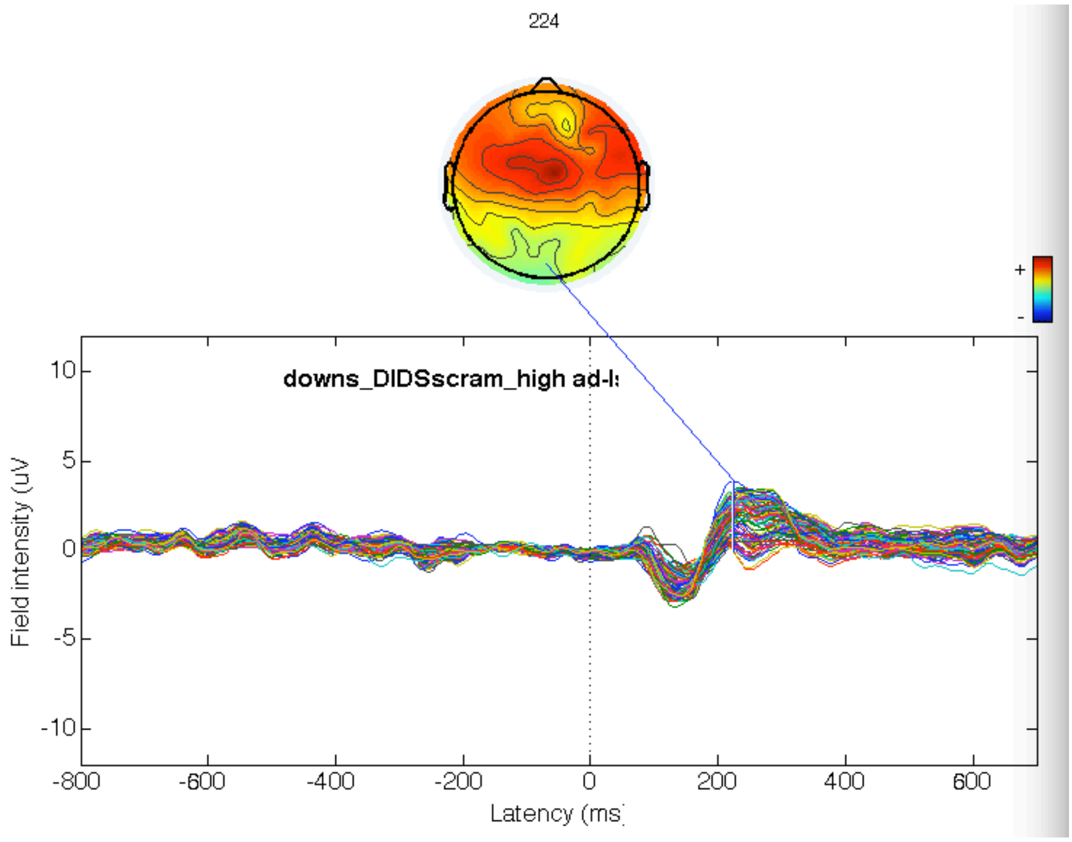

Figure 2.12. P3a for adults with DS who are higher scorers on the scrambled boxes task*.* Each line is the time course of a participant with DS. Red on the scalp map indicates positivity, the darker red the more positive the activity.

2.17 Post-processing

The pre-processing steps, and time-windows, are uniform across the chapters. The post-processing analyses, which are pertinent to each of the research questions and will be explained in the results chapters: 3, 4, 5 and 6.

3 Chapter 3. Exploring differences on selected EEG measures between adults with Down's Syndrome and typically developing controls

3.1 Aim

To use electroencephalographic measures (MMN, P3a, Pb) to compare adults with Down's Syndrome and typically developing controls, within a predictive coding framework.

3.2 Introduction

In this thesis, the Down's syndrome (DS) group is matched in age and gender to the typically developing (TD) control group. Consequently, age is inherently controlled for in between-group comparisons. The purpose of the initial between-groups comparison was to: 1. Confirm the presence of the ERPs, and 2. Assess the baseline electroencephalographic (MMN, P3a, P3b) differences between the groups, prior to deeper investigations based on: age (chapter 4), executive dysfunction (chapter 5) and cognitive decline (chapter 6). The electroencephalographic measures are elicited under a 'global-local' paradigm (Bekinschtein et al., 2009), which alters the context of simple tones to create a predictive hierarchy (Chennu, Noreika, et al., 2013). Consequently, the group comparisons can be considered within a predictive coding framework.

Predictive coding uses a hierarchical framework to economically deliver a stable, internal representation of the external environment (Jack & Hacker, 2014). The framework is economical and hierarchical in that top-down predictions constrain the processing of bottom-up sensory input, to the unexpected: 'prediction errors' (Friston, 2005). Within a predictive coding framework MMN and P300 (P3a and P3b) might be explained as prediction error signals (Friston, 2005; Garrido et al., 2007; Lieder et al., 2013; Wacongne et al., 2011; Wacongne, Changeux, & Dehaene, 2012). The global-local paradigm embeds auditory regularity at local (tone) and global (tone sequence) levels, the violations of which are termed ‘prediction errors’ (Bekinschtein et al., 2009). Violations at the ‘local’ level are detected in the absence of attention. The low-level, prediction errors manifest as MMN and P3a waveforms (Bekinschtein et al., 2009). Prediction errors at the ‘local’ level feed-forward to a temporally-extended ‘global’ level for pattern extraction (tone sequences) (Chennu, Noreika, et al., 2013). Violations at the ‘global’ level are detected when attention is paid; the resulting signal is a P3b waveform (Bekinschtein et al., 2009).

The literature comparing the electrophysiological measures of interest (MMN, P3a, P3b) between adults with DS and age- and gender- matched typically developing (TD) controls is limited, and out-dated. Previous research has suggested that people with DS show comparatively decreased amplitudes of the potentials: MMN (Arisi et al., 2012; César et al., 2010; Lalo et al., 2005), and P3b (Blackwood et al., 1988; César, Caovilla, Munhoz, & Ganança, 2010; Kakigi, Neshige, Matsuda, & Kuroda, 1994; Lalo, Vercueil, Bougerol, Jouk, & Debû, 2005; Medaglini et al., 1997; Seidl et al., 1997; St. Clair & Blackwood, 2013; Vieregge, Verleger, Schulze-Rava, & Kömpf, 1992; Wetter & Murphy, 1999), compared to TD adults. Therefore the present study would expect a similar pattern.

Although P300 comprises two potentials: ‘P3a’ and ‘P3b’ (Polich, 2007), in the literature, P3b has been much more extensively studied (Polich & Kok, 1995). As a result, explicit investigations of the P3a waveform in adults with DS have proved difficult to find. However, when investigating P300 with a P3b focus, Kakigi et al. (1994) reported a frontal shift in the DS group that was not evident in age-matched controls. The frontal shift could have been the result of a P3a dominated response, considering that the P3a component is fronto-centrally distributed (Polich, 2007). The early behavioural presentation of Alzheimer’s disease in DS seems to be weighted towards changes in cognitive functions underpinned by the frontal lobes (Ball et al., 2006; Ball, Holland, Treppner, Watson, & Huppert, 2008). Therefore, the frontal locus of P3a activity means that it could be of clinical relevance in early DS-AD. P3a is associated with distractibility and disinhibition, which could enhance the waveform as disinhibited behaviours develop, or diminish the waveform as neurons are lost from the frontal cortex, with aging and AD (Fjell & Walhovd, 2004). Of course, caution must be taken with suggestions that behavioural inhibition and inhibition of a sensory response (habituation) can be conflated.

The few previous studies which have compared people with DS and typically developing controls have predominantly employed a single canonical electrode approach to the analyses of P3b (Blackwood et al., 1988; César, Caovilla, Munhoz, & Ganança, 2010; Kakigi, Neshige, Matsuda, & Kuroda, 1994; Lalo, Vercueil, Bougerol, Jouk, & Debû, 2005; Medaglini et al., 1997; Seidl et al., 1997; St. Clair & Blackwood, 2013; Vieregge, Verleger, Schulze-Rava, & Kömpf, 1992; Wetter & Murphy, 1999). Single canconical electrode selection is based on where the event-related potential is typically maximal, for example Fz for MMN. However, the morphology of the DS brain is fundamentally different to that of the typically developing population with: reduced overall cortical volume (Lott, 2010); disproportionately diminished frontal lobes (Aylward et al., 1999); reduced neuronal density (Lott, 2010), amongst other features. The atypical brain morphology in DS may result in atypical electrodes having maximal electrophysiological responses.

This thesis acknowledges the potential confounds of the atypical DS brain by employing an across-scalp approach to explore the factors of: age (chapter 4), cognitive function (chapter 5) and cognitive decline (chapter 6). The across-scalp approach is called global field power (GFP). GFP is a reference- and polarity-independent technique, which evaluates electrophysiological data from all recording electrodes to determine the power of standard deviations in signal (i.e. ERPs) for each time point, within a given time frame (Lehmann & Skrandies, 1980). However, prior to investigations based on GFP, the time frames of interest must first be confirmed as encompassing the ERPs of interest. This is one the objectives for the present chapter. The potential time-windows of interest are proposed from the literature, as described in section 3.3. Within these proposed time-windows, the ERP presence is confirmed with spatio-temporal cluster analyses, following the procedure developed by

Chennu, Finoia, et al., (2013). The methodology of this procedure is described in section 3.5.2.

3.3 Time-windows

Spatio-temporal cluster analyses are used to confirm the presence of the ERPs, within the time-windows of interest (Chennu, Noreika, et al., 2013), section 3.5.2. Then, in the following chapters (4,5,6), the GFP maxima for the ERPs (MMN, P3a, P3b) will be measured as a function of time, within the time-windows of interest (Lehmann & Skrandies, 1980).

The chosen time windows are informed by the literature. According to the literature, the MMN waveform typically peaks between 100-200ms post-stimulus (Brønnick, Nordby, Larsen, & Aarsland, 2010; Friston, 2005; Hughes & Rowe, 2013; Naatanen, Jacobsen, & Winkler, 2005; Risto Näätänen & Kähkönen, 2009; Pekkonen, 2000; Pekkonen, Hirvonen, Jääskeläinen, Kaakkola, & Huttunen, 2001; Thönnessen et al., 2008; Wacongne et al., 2012).

As the name suggests, the P300 (P3a, P3b) waveform typically peaks around 300ms post-stimulus. However, the time-window can extend to as long as 1000ms post-stimulus for the processing of complex linguistic stimuli (Duncan et al., 2009). The P300 time-window is typically defined between 250-650ms post-stimulus, encompassing both earlier (P3a) and later (P3b) components of the potential (P300). Indeed, van Dinteren, Arns, Jongsma and Kessels (2014) performed a systematic review and meta-analysis of 75 studies which investigated P300 across the lifespan, which included an analysis of the latency values. *Figure 3.1.* is adapted from the article. As the figure (3.1.) displays, the majority of P300 latency values occur in the 250-400ms time frame, as the name (300ms) expects. In the context of the present study, P300 latency is typically increased for: 1. Older adults (Duncan et al., 2009; Kerr et al., 2010; Polich, 2007; Rossini et al., 2007; Schiff et al., 2008; Walhovd et al., 2008); and 2. Adults with DS (Blackwood et al., 1988; César, Caovilla, Munhoz, & Ganança, 2010; Kakigi, Neshige, Matsuda, & Kuroda, 1994; Lalo, Vercueil, Bougerol, Jouk, & Debû, 2005; Medaglini et al., 1997; Seidl et al., 1997; St. Clair & Blackwood, 2013; Vieregge, Verleger, Schulze-Rava, & Kömpf, 1992; Wetter & Murphy, 1999). Therefore, the latency ranges have been parsed to identify potential earlier (200-400ms) and later (400-650ms) components.

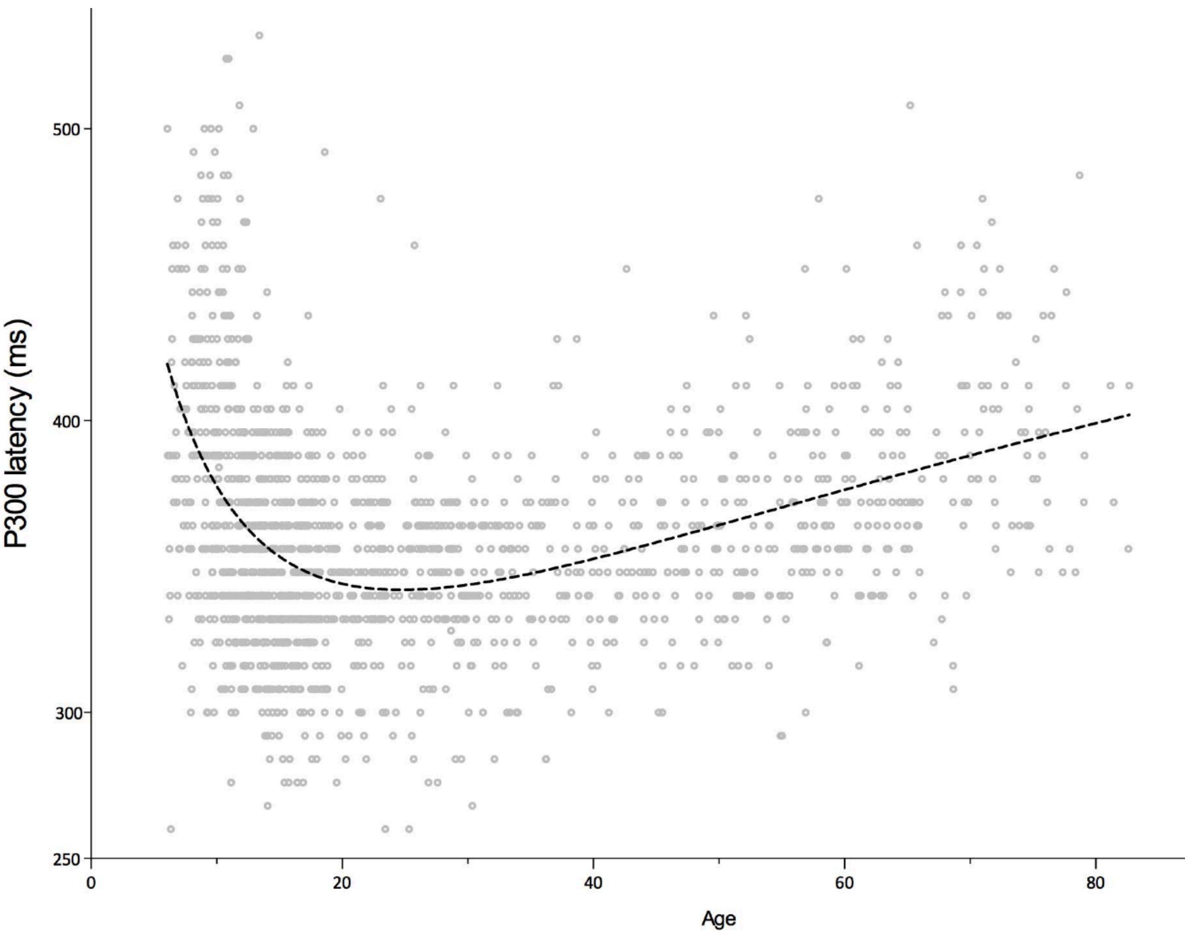

Figure 3.1. P300 latencies, across the lifespan, from 75 cross-sectional studies. Each data point represents an individual participant. The graph is adapted from van Dinteren et al. (2014), page 8.

The appropriateness of the proposed time-windows for GFP analyses, in the following chapters (4,5,6), is confirmed with the spatio-temporal cluster analyses in the present chapter (3), section 3.5.2, 3.6.2.

3.4 Hypotheses

Adults (DS, TD) are expected to generate significant clusters for the ERPs (MMN, P3a, P3b), within the proposed time-windows of interest.

Adults with DS will have significantly smaller MMN and P3b amplitudes, than age- and gender-matched TD controls.

Adults with DS will have significantly different P3a amplitudes than age- and gender-matched TD controls. The direction of the difference (smaller vs. larger) is unknown.

3.5 Methods

3.5.1 General methods

Full details of participant identification; neuropsychological assessments; EEG acquisition, paradigms and pre-processing, can be found in chapter 2, sections 2.5, 2.8, 2.14, 2.15 and 2.16.

3.5.2 Spatio-temporal cluster analyses

The aim of the cluster analyses was to calculate the ERPs (MMN, P3a, P3b) with subject-wise averages, for each condition. The cluster analysis procedure follows that developed by Chennu, Finoia, et al., (2013). A Monte Carlo procedure was used to: 1. Identify temporal clusters, and 2. Estimate the *p*-values of statistically significant differences in response between pairs of conditions: deviant vs. standard. The response to deviations, in the absence of active attention, generated 'local' MMN (negative directionality) and P3a (positive directionality) responses. The response to deviations, when active attentive processes were engaged, generated a 'global' P3b (positive directionality) response. A randomisation testing procedure was used to establish the statistical significance of the different clusters for each ERP. The steps for the Monte Carlo randomisation procedure were as follows:

1. The subject-wise condition averages were mixed and separated into two random samples.
2. Average ERPs were calculated for the random samples.
3. Steps 1 (randomisation) and 2 (resampling) were repeated 1000 times.
4. The original, and randomised, ERPs for each time-point were compared, to generate *t*-values and *p*-values.
5. The original, and randomised, ERPs were clustered based on contiguity and having *p* values of <.05.
6. The cluster-level *t*-values were retained.

7. The distribution of cluster-level *t*-values generated by the randomisation procedure was compared to the original ERPs, to calculate a non-parametric *p*-value, which is reported.

The result of the randomisation procedure is a Monte Carlo estimate of the statistical significance for the original clusters and ERPs. The method is used to control for family wise error and multiple comparisons (Maris, 2004; Maris & Oostenveld, 2007). The appropriate script can be found in appendix W.

The results of this analysis are used to confirm the ERPs of interest (MMN, P3a, P3b) within the time-windows of interest (100-200ms, 200-400ms, 400-650ms). The confirmation of the ERPs and time-windows forms the basis of the across-scalp GFP analyses in the forthcoming chapters (4,5,6), relative to the factors of interest: age, cognitive function, and cognitive decline.

3.6 Results

3.6.1 Participant demographics

36 adults with DS (22-55 years), and 39 TD controls (20-59 years), completed the cross-sectional phase of the study. Independent samples t-tests for Equality of Means were conducted, with Equality of Variances assumed ($p > .05$) to find that the participant group with Down's Syndrome (DS) and the typically developing (TD) control group did not significantly differ in age ($p = .15$). Equality of Variance was not assumed ($p < .05$) for group comparisons on hearing acuity. The number of tones identified from the Siemens Hear Check Screener assessed hearing acuity. An independent samples t-test for the Equality of Means found that the number of tones identified did not significantly differ between groups ($p = .12$). A chi-square test of independence was performed to examine the relationship between gender (male, female) and group (DS, TD) and found no significant relationship: X^2 (1, 75) = 2.24, $p = .134$. Please see table 3.1 for more details.

Group	N	Number of males	Number of females	Mean age (years)	*SD*	Mean number of tones heard	*SD*
Down's Syndrome	36	21	15	36.56	9.38	9.83	1.8
Controls	39	17	22	40.08	11.34	10.33	.70

Table 3.1. Participant demographics: sex, age and hearing acuity.

For the age- and gender-matched typically developing controls: the lowest IQ score, as assessed by the Kaufman Brief Intelligence Test, second edition (KBIT II), was 90; the lowest dementia-screening score, as assessed by the Addenbrooke's Cognitive Examination - Revised (ACE-R), was 88. Therefore, the group is considered as appropriate to be 'typically developing controls', for this study. The test values can be found in table 3.2. The comparable DS results can be found in chapter 5, section 5.6.1.1. A visualization of the spread and distribution of the groups' (DS, TD) KBIT II scores can be found in figure 3.2.

Variable	Minimum	Maximum	Mean	*SD*
Age (years)	20	59	40.08	11.43
KBIT II IQ composite score	90	136	111.56	11.58
ACE-R	88	100	95.36	3.68

Table 3.2. Test values for the age- and gender- matched TD controls.

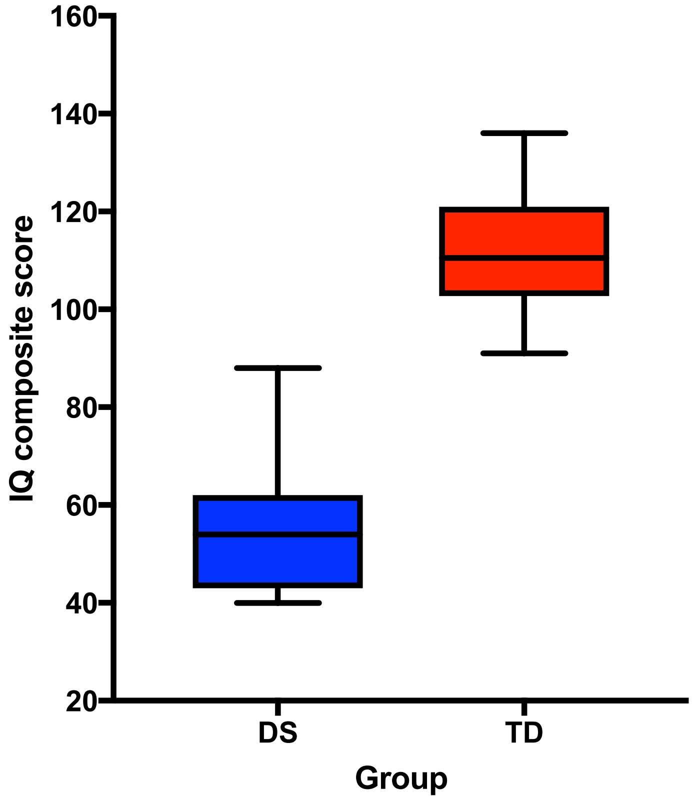

Figure 3.2. Boxplots of the groups' (DS, TD) IQ composite scores, as measured by the KBIT II, and standardized by age.

The participant demographics described in this section apply to each of the results chapters.

3.6.2 *Spatio-temporal cluster analyses*

3.6.2.1 *MMN*

Participants showed group-wise (controls, DS) statistically significant clusters: the response to deviant tones within 100-200ms (MMN response) significantly differed to the standard tone response. The age- and gender- matched typically developing (TD) controls showed the difference at *p* = 5.6e-31 (p<.001) level, the participants with DS showed the difference at a *p* = .0004 level. The interaction between groups (controls, DS) showed a significant cluster difference, for an MMN response, at between 98-118ms, with a peak at 102ms, *p* = .00124. In summary, the MMN response was significantly larger for control participants than participants with DS. This comparison is visualised in figure 3.3.

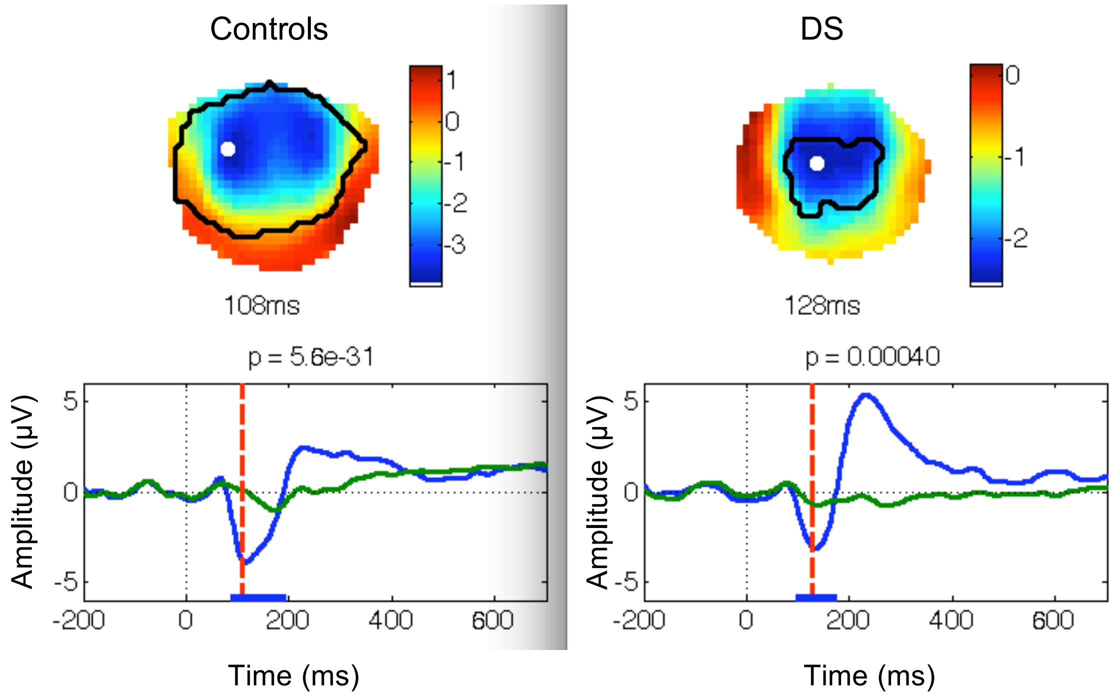

Figure 3.3. The image on the left shows the age- and gender- matched controls group. The image on the right shows the participants with DS group. The bottom half of the images maps the time course, by group. The green line shows the response to standard tones and the blue line indicates responses to deviant tones, the amplitude difference of which produces an MMN response. The horizontal, thick blue line shows the temporal extent of the

significant cluster of contiguous time points where the response to deviants (within an MMN context) was greater than standards. The significance of the difference for controls is p = 5.6e-31, and for participants with DS is p = .0004. The vertical, dashed red line indicates the time point in the cluster where the ERP was maximal. These time points are mapped out on the scalp maps, in the upper half of the image. For controls the time point was 108ms, for participants with DS the time point was 128ms. On the scalp map, blue indicates electrodes with more negative ERP amplitude in response to deviant tones compared to standard tones, and red indicates electrodes with more positive ERP amplitude in response to deviant tones compared to standard tones. The black line indicates the spatial location of the significant difference cluster. The white circle indicates the electrode where the difference is maximal.

3.6.2.2 Earlier P300

Participants showed group-wise (controls, DS) statistically significant clusters: the response to deviant tones within 200-400ms (P300 response) significantly differed to the standard tone response. The age- and gender- matched TD controls showed the difference at *p* = 5.6e-31 (p<.001) level, the participants with DS showed the difference at a *p* = 1.2e-26 (p<.001) level. The interaction between groups (controls, DS) showed a cluster difference, at between 382-398ms, with a peak at 394ms, *p* = .01. In summary, adults with DS showed a large P3a response in this time period. However, the parietal locus of the P3 response in controls, combined with the later onset (340ms), presents this time period (200-400ms) as dominated by a P3b response, for TD controls. This comparison is visualised in figure 3.4.

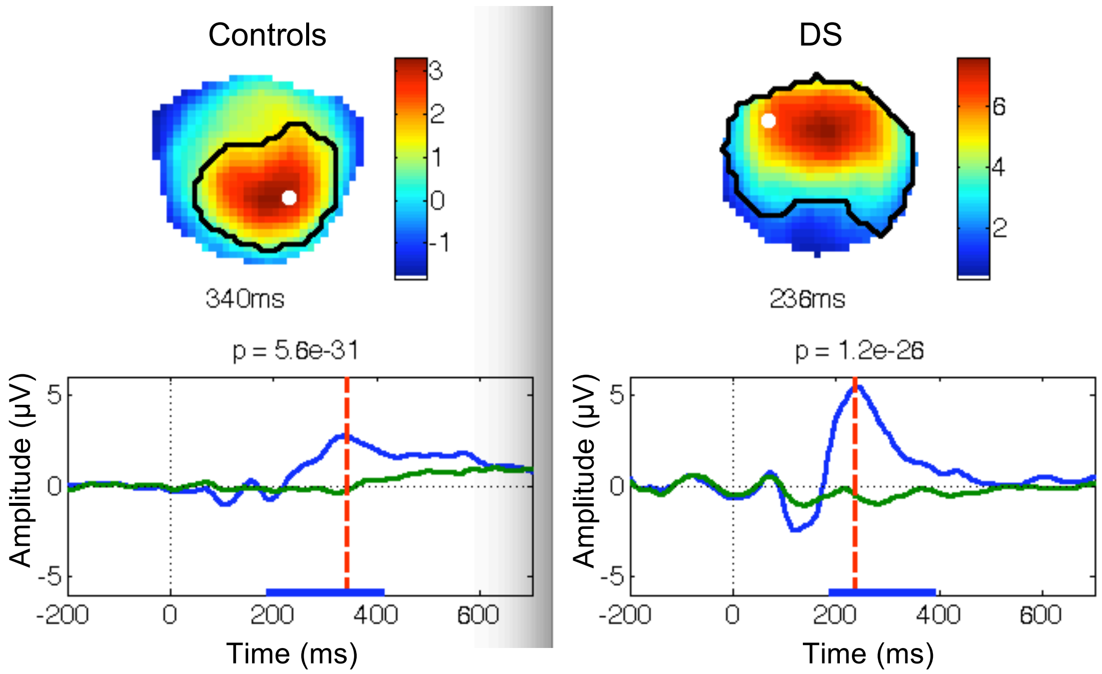

Figure 3.4. The image on the left shows the age- and gender- matched controls group. The image on the right shows the participants with DS group. The bottom half of the images maps the time course, by group. The green line shows the response to standard tones and the blue line indicates responses to deviant tones. The horizontal, thick blue line shows the temporal extent of the significant cluster of contiguous time points where the response to

deviants was greater than standards. The significance of the difference for controls is p = 5.6e-31, and for participants with DS is p = 1.2e-26. The vertical, dashed red line indicates the time point in the cluster where the ERP was maximal. These time points are mapped out on the scalp maps, in the upper half of the image. For controls the time point was 340ms, for participants with DS the time point was 236ms. On the scalp map, blue indicates electrodes with more negative ERP amplitude in response to deviant tones compared to standard tones, and red indicates electrodes with more positive ERP amplitude in response to deviant tones compared to standard tones. The black line indicates the spatial location of the significant difference cluster. The white circle indicates the electrode where the difference is maximal.

3.6.2.3 Later P300

In an attempt to explore whether the participants with DS displayed the later P3 component (P3b), the 400-650ms window was analysed for this group. The participants with DS did not show a significant cluster in this time-window, indicative of a P3b response. This is visualised in figure 3.5. In summary, the participant groups showed inverse patterns. The participants with DS showed a large P3a response but no significant P3b response, whereas control participants showed a significant P3b response but no significant P3a response.

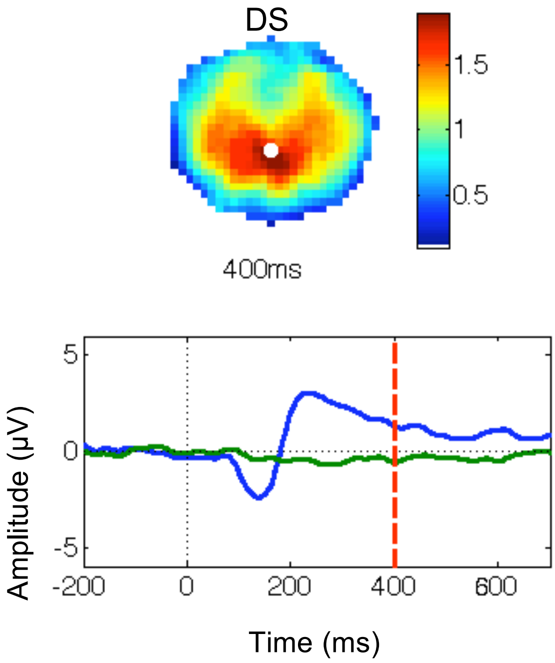

Figure 3.5. The image shows the participants with DS group. The bottom half of the image maps the time course. The green line shows the response to standard tones and the blue line indicates responses to deviant tones. The vertical, dashed red line indicates the time point in the cluster where the ERP was maximal. However, there were no significant clusters in this time-frame. Nevertheless, this time point of maximal difference is mapped out on the scalp map, in the upper half of the image. For the participants with DS the time point was 400ms. On the scalp map, blue indicates electrodes with more negative ERP amplitude in response to deviant tones compared to standard tones, and red indicates electrodes with more positive ERP amplitude in response to deviant tones compared to standard tones. The white circle indicates the electrode where the difference is maximal.

3.7 Cluster analysis confirmation of time-windows

The time-windows chosen from the literature (section 3.3) were explored in the present chapter as the time frames in which statistically significant MMN, P3a, and P3b clusters were expected for the ERPs.

Following the spatio-temporal cluster analyses the post-stimulus time-windows were confirmed as follows: MMN – 100-200ms, P300 – 200-400ms. The 200-400ms time-window was dominated by a P3b response for the control participants and a P3a response for the participants with DS. The later P300 time-window (400-650ms) was also explored for adults with DS. However, no significant clusters for a P3b response were found between 400-650ms. Nevertheless, there is a-priori evidence that P3b is affected by typical and pathological aging (chapter 1, section 1.12.2). Therefore, in relation to these factors, P3b should continue to be explored in the following chapters (4,5,6).

3.8 Discussion

In the present study, participants with DS showed significantly smaller MMN responses than age- and gender-matched TD controls. This result is in agreement with previous research which has compared the potential (MMN) between the groups (DS, controls) (Arisi et al., 2012; César et al., 2010; Lalo et al., 2005). Previous studies have eluded to a frontal shift in P300 for children (Kaneko et al., 1996b) and adults (Kakigi et al., 1994; Vieregge et al., 1992) with DS. The present study unpicks this enlarged frontal response to find a significantly enhanced P3a for the participants with DS.

For control participants, the P300 response is predominantly parietal in nature, which suggests more P3b contributions, to the response, than P3a (Polich & Kok, 1995). This finding is juxtaposed against the lacking P3b response for participants with DS, in the presence of a large P3a response. P300 can be considered as both the capture (P3a) and maintenance (P3b) of attention. Within this conceptualisation, we can consider the relative strengths and weaknesses of the DS cognitive profile. A cognitive examination of 86 adults with DS (16-34 years) found that although episodic memory performance is generally poor in DS, controlling attention and encoding information are especially impaired (de Sola et al., 2015). This cognitive profile ties into the electrophysiological finding that attention is captured (enlarged P3a), but not necessarily maintained and encoded (no P3b) in DS.

The lacking P3b response in DS could be a product of the attentional demands required to elicit the response. Whilst MMN is pre-attentional and automatic (Duncan et al., 2009); P3b requires attention and the active maintenance of working memory (Polich, 2007). Most people with DS have attentional and cognitive deficits. In this study, these attentional deficits are reflected in the indistinguishable P3b response from baseline, for participants with DS, at a group level. This lacking response is reflected in how the participants completed the task. At the end of each block, participants were asked to report what group of sounds they heard **alot** and what group(s) they heard **sometimes**, to maintain attention and develop a P3b response. The majority of participants with DS were unable to report the distinction, and instead focused their report on the rare, inter-aural deviant. This rare deviant focus is congruent with an enlarged P3a response. In contrast, all the control participants perceived and reported the distinction, to show a P3b response. Furthermore, a P3a response is generated in the absence of a task, whereas P3b generation is task dependent (Polich & Criado, 2006). This distinction maps onto the behavioural findings that the overwhelming majority of adults with DS were not performing the task (P3a), whereas all the TD controls were easily performing the task (P3b).

The deviant, inter-aural stimulus, which leads to a P3a response, is infrequent but repeated, as part of a group. Consequently, the involuntary attention switch response should eventually be habituated; then contextualised by the task, for a P3b dominated response. This effect is seen in the TD control participants. However, for the adults with DS, this habituation process does not occur, leading to a consistently large P3a response. P3a has a fronto-central locus (Polich, 2007), and has been suggested as an index of distractibility and disinhibition (Fjell & Walhovd, 2004). Inhibitory control is an executive function, under-pinned by the frontal lobes. The early behavioural presentation of AD in DS is weighted towards changes in cognitive functions underpinned by the frontal lobes (Ball et al., 2006; Ball, Holland, Treppner, Watson, & Huppert, 2008). Therefore the increased P3a response in DS could be interesting from an executive dysfunction perspective, associated with early signs of AD. However, we must take care not to conflate the two, as behavioural inhibition and the habitual inhibition of a sensory response are dissociable mechanisms. The habituation hypothesis, and other potential mechanisms, are explored further in chapter 5.

Perception can be viewed as a testable hypothesis (Jack & Hacker, 2014), whereby perceptive ‘predictions’ are challenged by ‘prediction errors’. In terms of predictive coding, perceptive processing is constrained to instances when the top-down ‘prediction’ is challenged by bottom-up ‘prediction errors’ (Friston, 2005). The feedback loops are functionally asymmetric, whereby bottom-up ‘prediction errors’ drive the formation of top-down ‘predictions’, which in turn modulate the processing of bottom-up stimuli (Friston, 2005). Predictive coding can be used to contextualise ERPs (MMN, P3a, P3b) as ‘prediction errors’ (Garrido et al., 2007; Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007; Wacongne et al., 2012). Within this framework, MMN and P3a are low, ‘local’ level violations of the prediction which occur in the absence of attention (Bekinschtein et al., 2009). The uptake of these low, ‘local’ level violations into a ‘global’ framework, updates the ‘prediction’ (Chennu, Finoia, et al., 2013). The ‘global’ framework requires the active maintenance of attention and if violated, results in a P3b waveform (Bekinschtein et al., 2009). To place the findings of the present study within a predictive coding framework: for participants with DS the low-level, attention independent, prediction error that generates MMN and P3a responses, is present. However, the higher order, attention dependent, prediction error that generates P3b is not discernible from baseline in DS. This suggests a deficit in DS for feeding-forward from the attention-independent to the attention-dependent system, which is temporally extended to allow for pattern extraction.

A counter proposal for the predictive coding hypothesis of MMN generation is synaptic habituation, in that repeated stimulation reduces amplitudes and novel stimulation recovers the reaction (May & Tiitinen, 2010). Indeed, adaptation and short-term plasticity are essential features of cortical synapses (Calford, 2002) and, more specifically, the functioning of the auditory cortex (Brosch & Schreiner, 2000). However, Wacongne et al., (2012) argues that synaptic habituation and predictive coding are complimentary rather than contradictory hypotheses. Wacongne et al., (2012) presents a model of spiking excitatory and inhibitory neurons, which are distinctly attuned for: environmental input, prediction and prediction errors, and modulated by NMDA receptor synaptic transmission. Wacongne et al., (2012) argues strongly for an active, predictive system rather than a passive effect. As such, synaptic habituation is proposed as a necessary but not sufficient mechanism to generate MMN responses (Wacongne et al., 2012).

The present study uses the information gained about ERP time-windows in this chapter to inform GFP analyses in the upcoming chapters (4,5,6). The primary benefit of using GFP analyses is that the whole brain is considered, bypassing issues of differing sites of maximal potential because of the atypical brain anatomy in DS (Lott, 2010).

3.9 Summary

In summary, participants with DS showed significantly smaller MMN responses than age- and gender- matched controls. This finding is consistent with the literature. However, a novel finding of the study is that while the controls showed a standard P3b response the participants with DS showed a very large P3a response.

Having established the waveforms at a group level (the group with DS and the TD controls), we can now explore the effects of: age (chapter 4), executive dysfunction (chapter 5), and cognitive decline (chapter 6), using whole-brain GFP analyses.

4 *Chapter 4. Investigating whether EEG evidence supports the accelerated aging hypothesis of Down's Syndrome*

4.1 Aim

To use electroencephalographic measures as a means of testing the accelerated brain aging hypothesis in Down's Syndrome.

4.2 Introduction

People with Down's Syndrome (DS) are hypothesised to experience accelerated aging. This hypothesis is supported across several physiological systems: from earlier menopause to premature skin wrinkling (see Zigman, 2013 for a review). This thesis is concerned with testing the hypothesis that people with DS experience accelerated aging to the neurological system, with the event-related potentials (ERPs): mismatch negativity (MMN) and P300 (P3a, P3b). Accelerated aging in DS is, importantly, characterised by early-onset Alzheimer's disease (AD) (Zigman, 2013). Age is the primary, and only irrefutable, risk factor for AD. Therefore, in the search for meaningful markers of pathological aging (AD), we must first acknowledge the contributions of typical aging (Humpel, 2011).

Sensory memory and perceptual accuracy decline with typical aging (Demiral et al., 2012; Fakhri et al., 2012; Lauzière et al., 2012; Stewart & Wingfield, 2009). Therefore, as MMN can be used to index sensory memory (Pekkonen et al., 1996), the relationship between this ERP and typical aging has been tested. Previous studies of electrophysiological aging, with the typically developing (TD) population, have generally agreed that MMN amplitudes decrease with increasing age (Alain, McDonald, Ostroff, & Schneider, 2004; Alain & Woods, 1999; Bertoli, Smurzynski, & Probst, 2002, 2005; Cooper, Todd, McGill, & Michie, 2006; Czigler, Csibra, & Csontos, 1992; Horváth, Czigler, Birkás, Winkler, & Gervai, 2009; Horváth, Czigler, Winkler, & Teder-Sälejärvi, 2007; Karayanidis et al., 1995; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Pekkonen et al., 1996; Pekkonen, 2000; Rimmele, Sussman, Keitel, Jacobsen, & Schröger, 2012; Schiff et al., 2008; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015; Woods, 1992). There has been some opposition to a relationship between MMN amplitude and age (Amenedo & Díaz, 1998), but a recent meta-analysis concluded that, on balance, there was a robust relationship (Cheng, Hsu, & Lin, 2013). Although there is some suggestion that MMN latencies increase with increasing age (Bertoli et al., 2002, 2005; Cooper et al., 2006; Tsolaki et al., 2015), the amplitude relationship is considered more robust (Schiff et al., 2008).

Schiff et al. (2008) go on to suggest that later, more cognitive components, such as P3b, are potentially more sensitive to age effects than MMN. In chapter 3, a consistent P3b effect was found in the earlier time window (200-400ms), for the TD adults. However, for the DS group, the earlier time window was dominated by a P3a response and no consistent P3b effect was found in the later time window (400-650ms). Nevertheless, P3b latency is typically increased for older adults (Duncan et al., 2009; Kerr, van Albada, Rennie, & Robinson, 2010; Polich, 2007; Rossini, Rossi, Babiloni, & Polich, 2007; Schiff et al., 2008; Walhovd, Rosquist, & Fjell, 2008). Consequently, the inconsistent P3b effect could be the result of age effects, and thus tie into an accelerated aging hypothesis of DS. Accordingly, this chapter will also explore age effects in the 400-650ms time-window, for the adults with DS.

P300, specifically the P3b component, has been linked with typical adult aging from physiological, cognitive and electrophysiological perspectives. Physiologically, the parietal cortex, which enable P3b generation, shows reduced thickness for older adults (Lemaitre et al., 2012). Cognitively, P3b indexes attentive and memory processes, which are often compromised for older adults (Quigley et al., 2010; Quigley & Müller, 2014). Electrophysiologically, P3b shows decreased amplitudes and increased latencies for TD older adults (Duncan et al., 2009; Kerr, van Albada, Rennie, & Robinson, 2010; Polich, 2007; Rossini, Rossi, Babiloni, & Polich, 2007; Schiff et al., 2008; Tsolaki et al., 2015; Walhovd, Rosquist, & Fjell, 2008).

Again, P3b has been the focus of P300-aging research (Duncan et al., 2009; Kerr et al., 2010; Polich, 2007; Rossini et al., 2007; Schiff et al., 2008; Tsolaki et al., 2015; Walhovd et al., 2008). Nevertheless, P3a and P3b waveforms are strongly correlated, and have been demonstrated to correlate with age in the same way as one-another: reducing amplitudes and increasing latencies (Walhovd & Fjell, 2001). Furthermore, P3a has been presented as having a linear relationship with age (Fjell & Walhovd, 2004); a relationship that is potentially stronger than that of the P3b component with age (Fjell & Walhovd, 2004).

The suggestion of decreased MMN, P3a and P3b amplitudes for older adults plays into an "under-recruitment" model of typical aging. The "under-recruitment" model equates poorer performance with reduced activity. Indeed, fMRI studies with older adults have suggested that during memory encoding (Logan et al., 2002) and retrieval (Cabeza et al., 2004) activity is reduced in the prefrontal cortex and medial temporal lobes, respectively.

A topographical study of P300 distribution found that, with age, sources move to have a frontal distribution, and the maximum intensities gain a temporal locus (Tsolaki et al., 2015). In addition, MMN may present more parietally with increasing age (Anderer, Semlitsch, & Saletu, 1996). These topographical findings present an argument for whole brain, rather than single canonical electrode, analyses when exploring the relationship between the ERPs and typical aging. The atypical DS brain morphology (Lott, 2010), presents a further argument as to why atypical electrodes may be maximal for the ERPs, rendering single canonical electrode analyses inappropriate.

This thesis has chosen to extract the global field power (GFP) maxima, and associated latencies. GFP is a reference- and polarity-independent technique, which evaluates electrophysiological data from all recording electrodes to determine the power of deviations (i.e. ERPs), within a given time frame (Lehmann & Skrandies, 1980). The time at which the GFP maxima (largest deviation) occurs can indicate the latencies of ERPs (Skrandies, 1990).

GFP is extracted from the post-stimulus time frames of interest, for each ERP: MMN – 100-200ms, P300 – 200-400ms. In this time-window (200-400ms) the P300 response is dominated by a P3a response for adults with DS, and a P3b response for the TD controls. In an exploration of the potential effects of age on P3b generation, the later time window (400-650ms) will also be investigated for adults with DS.

We would expect the electrophysiological hallmarks of typical aging: reducing amplitudes, akin to GFP maxima, and increasing latencies, to be exacerbated for adults with DS, within an accelerated aging framework.

4.3 Hypotheses

1. Older TD adults will show smaller GFP maxima and longer latencies (MMN, P3b) than younger adults, in their group.

2. Older adults with DS will show smaller GFP maxima and longer latencies (MMN, P3a, P3b) than younger adults, in their group.

3. With age, adults with DS will show a greater decrease in GFP maxima (MMN, P3b), and greater increase in latencies, than TD controls.

4.4 Methods

Full details of participant identification; neuropsychological assessments; EEG acquisition; paradigms and pre-processing, can be found in chapter 2, sections 2.5, 2.8, 2.14, 2.15 and 2.16.

The data was pre-processed using custom MATLAB scripts, as described in chapter 2, section 2.16. The GFP maxima were extracted from post-stimulus time frames where the ERPs of interest would be expected: MMN: 100-200ms, P300: 200-400ms, 400-650ms. Please see appendix X for the custom script used to gain the GFP values. Please see chapter 3, sections 3.3, 3.7 for more details on the time windows. The GFP maximum and latency values for each ERP time-window, and for each participant, were exported to SPSS for aging analyses.

In analyses where age is not handled as continuous variable, a ‘younger’ and ‘older’ adult dichotomy is used, with the split at 40 years old. Research by Annus et al (2015) informed the dichotomy. The research used a radioactive analogue of thioflavin: selective carbon–11 labelled radioisotope Pittsburgh Compound B (11C-PIB). PIB binds to beta-amyloid (Aβ), which allows this composite of senile plaques to be visualized in a Positron Emission Tomography (PET) scan. Previous research, using this technique, has suggested that people with DS begin to exhibit abnormal PIB binding from the age of 39 years old (Annus et al., 2015), and consistently in the 40s (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Sabbagh et al., 2011). This sigmoidal relationship between age and abnormal binding is visualised in figure 4.1 (*from* Annus et al., 2015). This qualitative shift at the age of 40 informed the dichotomy for the present aging analyses.

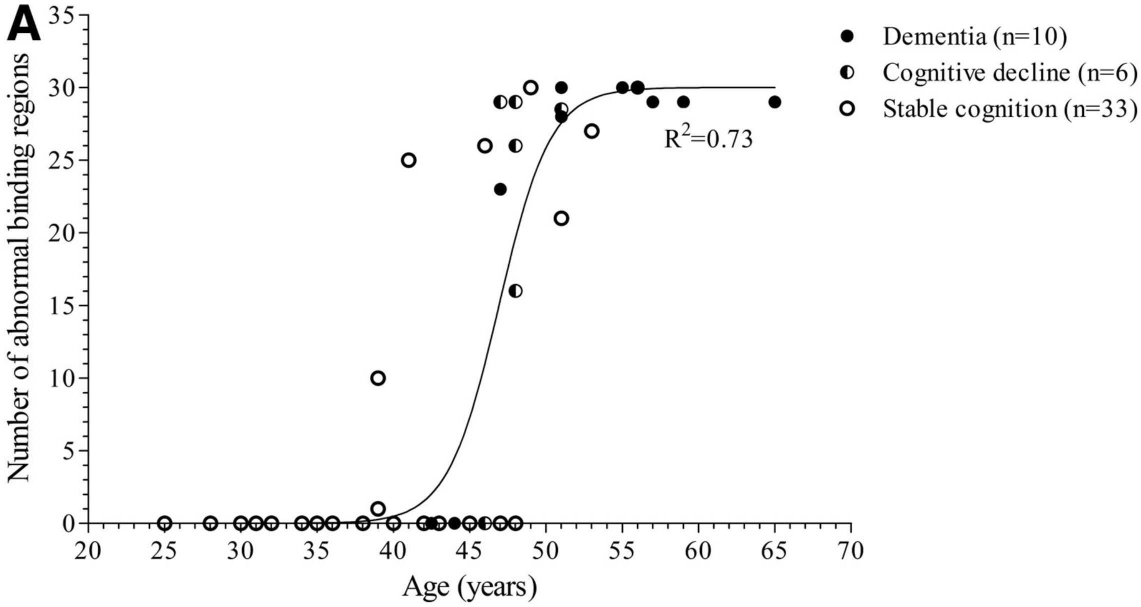

Figure 4.1. Taken from Annus et al., (2015) page 4, figure A: The sigmoidal relationship between age and abnormal PIB binding. The dichotomy begins around age 40 (years old).

For a full explanation of the methods used, including: recruitment, data acquisition and pre-processing, please see chapter 2.

4.5 Results

4.5.1 Participant demographics

The participant groups (DS, TD) were matched for age and sex, as summarized in table 4.1. For a detailed review of the participant (DS, TD) demographics, please see chapter 3, section *3.5.1. Participant demographics.*

Group	N	Number of males	Number of females	Mean age (years)	SD
Down's Syndrome (DS)	36	21	15	36.56	9.38
Typically Developing (TD) Controls	39	17	22	40.08	11.34

Table 4.1. Participant demographics: sex and age.

4.5.2 Correlations with age – within groups

The Shapiro-Wilk Test of Normality indicated that the GFP maxima and latencies for all the associated ERPs (MMN, P3a, P3b), for both groups (DS, controls), significantly differed to the normal distribution ($p < .05$). Therefore Non-Parametric, Spearman's Rank-Order correlations were used. Age did not significantly correlate with the standardized IQ scores for participants with DS: $r = .244$, $p = .152$, or controls: $r = .005$, $p = .978$. There were also no relationships between age and gender for participants with DS: $r = .022$, $p = .9$, or controls: $r = .246$, $p = .132$. Therefore, neither IQ nor gender will be considered further in this exploration of aging effects. Furthermore, based on the aging hypotheses being highly directional, the subsequent analyses are one-tailed. To correct for multiple comparisons, the Bonferroni correction is applied at $p < .02$. This level is based on the three ERPs (MMN, P3a, P3b) being clustered in families of GFP maximum (µV^2) and latency (ms): $p < .05/3 = 0.02$ (2 d.p.). An exploration of each GFP maxima and latency found that either: 1. There were no statistical outliers for the DS or control groups, as no participant was >3 standard deviations from the mean, or 2. If there were outliers, a sensitivity analysis revealed that the results were unchanged by their presence or absence, so they were retained in the analyses. For more details on the results of the sensitivity analysis please see appendix Y.

For participants with DS, the GFP maximum in the 100-200ms range (MMN) negatively correlated with age: *r* = - .385, *p* = .010. The latency of the GFP maximum (MMN) positively correlated with age: *r* = .367, *p* = .014. All other correlations between age and ERPs, for DS and controls, failed to reach significance (*p* > .02). Please see tables 4.2 and 4.3 for the correlational analyses for each ERP, by group, and Figure 4.2 for visualization.

Group	GFP maxima time-windows (ms)	Associated ERP	Mean GFP Maxima (μV^2)	*SD*	Correlation values with age	
					r	*p*
DS	100-200	MMN	5.97	5.39	-.385*	.010
	200-400	P300 (a)	9.87	7.99	-.191	.132
	400-650	P300 (b)	3.79	3.55	-.101	.279
Controls	100-200	MMN	11.32	6.83	.261	.054
	200-400	P300 (b)	8.39	7.21	.060	.358

Table 4.2. Spearman's Rank-Order correlations (one-tailed), by group (DS, controls), between age and ERP GFP maxima (MMN, P3a, P3b); all values are rounded to 3 s.f.; * indicates correlations which are significant at *p* < .02 level.

Group	GFP maxima time-windows (ms)	Associated ERP	Mean Latencies of GFP Maxima (ms)	*SD*	Correlation values with age	
					r	*p*
DS	100-200	MMN	131.89	18.1	.367*	.014
	200-400	P300 (a)	251.67	49.28	.144	.201
	400-650	P300 (b)	476	65.32	.182	.144
Controls	100-200	MMN	125.44	17.3	.013	.469
	200-400	P300 (b)	293.54	57.86	.024	.442

Table 4.3. Spearman's Rank-Order correlations (one-tailed), by group (DS, controls), between age and ERP latencies (MMN, P3a, P3b); all values are rounded to 3 s.f.; * indicates correlations which are significant at *p* < .02 level.

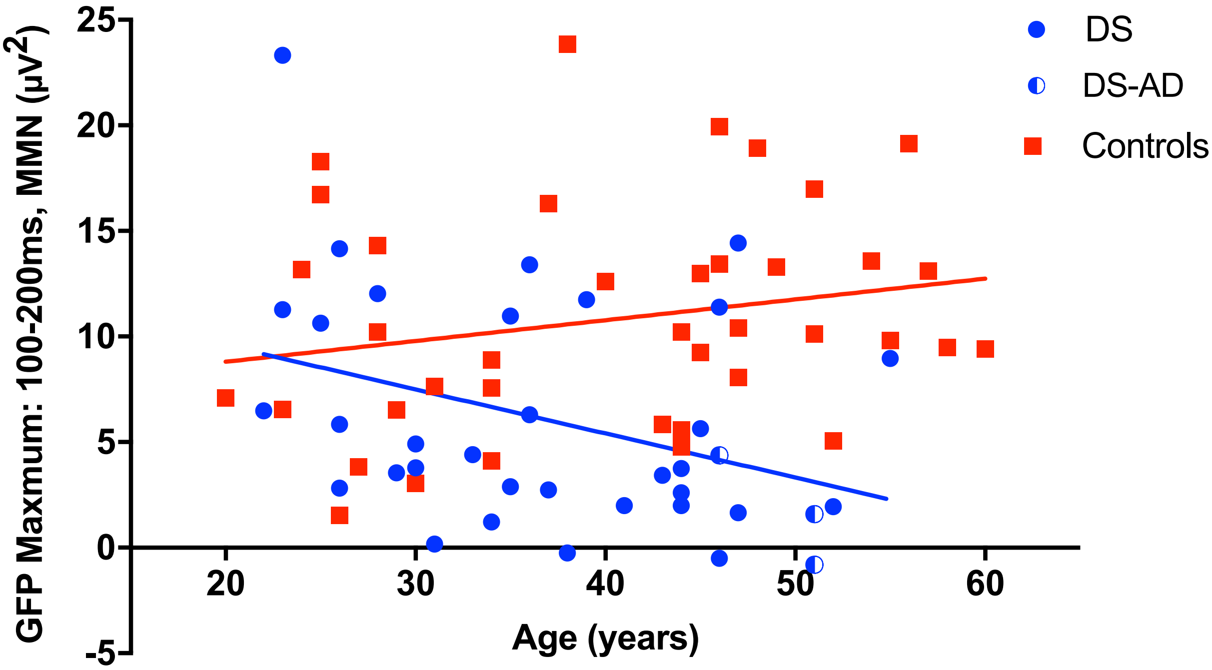

Figure 4.2. Scatterplot of participants' age (DS and age- and gender-matched typically developing controls), against GFP Maximum: 100-200ms, MMN (μV^2). The figure shows a significant effect of age for participants with DS but not controls. The MMN for adults with DS-AD sits within the range of responses for older adults with DS (no AD).

4.5.3 Correlations with age – between groups

Only the ERPs that significantly correlated with age at a within-group level (GFP maximum and latency - MMN) will be explored at a between-group level.

ANCOVAs were conducted to assess whether there were group (DS, controls) by age interactions with GFP maximum for MMN: $F(1) = 7.318$, p = .009, and MMN latency: $F(1) = 2.848$, p = .096.

The nature of the significant group by age interaction, with GFP maximum for MMN, was further explored with an independent samples t-test, using a dichotomy of 40 years old. Previous research has suggested that at the age of

40 adults with DS begin to show abnormal PIB binding, lending itself to be the dichotomous age of ‘younger’ vs. ‘older’ in this study. For the analysis, Equality of Variances was assumed (p > .05). Younger participants did not significantly differ, between groups (DS, controls), in GFP maximum (MMN): $t(37) = -1.511$, $p = .139$. However, older participants with DS had a significantly smaller GFP maximum for MMN (M = 4.16, *SD* = 4.31) than older controls (12.35, *SD* = 7.44): $t(34) = -3.820$, $p = .001$. Please see Table 4.4 for more group details.

Dichotomy	Group	N	Mean GFP maximum between 100-200ms, MMN (μV^2)	*SD*	*SE*
Younger (< 40 years old)	DS	21	7.26	5.80	1.27
	C	18	10.12	6.03	1.42
Older (> 40 years old)	DS	15	4.16	4.31	1.11
	C	21	12.35	7.44	1.62

Table 4.4. Details of the dichotomous groups (younger vs. older), where appropriate the values are rounded to 2 d.p

4.6 Discussion

This chapter aimed to address whether ERPs can be used to investigate the accelerated neurological aging hypothesis of DS.

At a within group analysis level the key findings were, for participants with DS: the GFP maximum for MMN negatively correlated with age and MMN latency positively correlated with age. All other ERP with age correlations, for DS and controls, failed to reach significance.

The pattern seen with aging in DS, of reducing GFP maxima for MMN, and increasing latencies, is inline with the typical ERP-aging literature (Alain, McDonald, Ostroff, & Schneider, 2004; Alain & Woods, 1999; Bertoli, Smurzynski, & Probst, 2002, 2005; Cooper, Todd, McGill, & Michie, 2006; Czigler, Csibra, & Csontos, 1992; Horváth, Czigler, Birkás, Winkler, & Gervai, 2009; Horváth, Czigler, Winkler, & Teder-Sälejärvi, 2007; Karayanidis et al., 1995; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Pekkonen et al., 1996; Pekkonen, 2000; Rimmele, Sussman, Keitel, Jacobsen, & Schröger, 2012; Schiff et al., 2008; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015; Woods, 1992). The lacking relationship with age in the control group, however, could be a product of youth. When Tsolaki et al. (2015) explored typical aging with MMN and P3b, comparisons were made between younger adults, aged 25-40 years, and older adults, aged 60+ years old. With this dichotomy, Tsolaki et al. (2015) found a significant effect of aging. In contrast, the oldest control participant in the present study was 59 years old. As a consequence of selecting a control group that is age-matched to the DS group, the ‘older’ cohort is potentially still too young to demonstrate substantive aging effects, as measured with electrophysiology. This interpretation could lend credence to the accelerated aging hypothesis of DS because, in stark contrast, their ‘older’ cohort demonstrated aging effects, as measured by MMN.

This suggestion of accelerated aging is reinforced at the between group analysis level: whilst younger participants (DS and controls) had similar GFP maxima (MMN); older participants with DS had significantly smaller GFP maxima (MMN) than older controls. This presents a case that the aging effect seen within the DS group is driven by the over 40s. This finding is complementary to the amyloid-binding literature, which shows a sigmoidal relationship between age and abnormal binding, focused around 40 years (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Sabbagh et al., 2011). The relationship between abnormal binding and the ERPs is explored further in chapter 6.

Whilst, at the within group level both the GFP maximum and latency for MMN significantly correlated with DS age. In contrast, when comparing aging between groups (DS, controls), only the GFP maximum for MMN withstood correction. If we consider the wider literature, which agrees on a relationship between age and MMN amplitude, akin to GFP maximum, but disputes whether MMN latency is also effected by age (Pekkonen et al., 1996; Pekkonen, 2000; Schiff et al., 2008), this is perhaps less surprising.

There are challenges explaining the differential age effects on MMN for adults with DS and TD controls in terms of the accelerated aging hypothesis. The primary issue is the inextricable link between AD and age, which is exacerbated by the consistent development of AD pathology for adults with DS over the age of 40 (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Sabbagh et al., 2011). Therefore, the observed effects of aging on MMN for the DS group could be attributable to the development of AD pathology rather than to a process of accelerated aging. Unfortunately, the cause of the observed age effects cannot be disentangled within the limitations of the present thesis.

Whether of not the participants with DS are demonstrating accelerated aging, it is surprising that the well-characterised P3b component did not demonstrate aging effects with this group. This could, however, be a product of the differing attentional requirements to elicit both ERPs. Whilst, MMN is pre-attentional and automatic (Duncan et al., 2009); P3b requires attention and the active maintenance of working memory (Polich, 2007). Most people with DS have attentional and cognitive deficits, which could lead to P3b compromise. Indeed, chapter 3 showed that the P3b response in DS was indistinguishable, from baseline, at a group level. Therefore, P3b was perhaps too variable within group to demonstrate a cohesive aging effect. The P300 component is further discussed in Chapter 5, which explores these more cognitively driven ERPs within a wider context of participants' executive functioning.

The "under-recruitment" model of aging equates poorer performance with reduced activity. This would play into a reduction in ERP amplitude, for older adults. In DS, not only do dendritic numbers increase at a slower rate during childhood but they also decline at a faster rate in adulthood (Takashima, Iida, Mito, & Arima, 1994). Dendrites are essential for synaptic functioning (Kasai et al., 2003; Sorra & Harris, 2000), and EEG measures summed post-synaptic potentials (Luck, 2005). Therefore, from a physiological perspective, one would expect an accelerated alteration to the EEG recordings. In the present study, age effects were limited to one ERP component (MMN).

4.7 Summary

The study investigated electrophysiological measures (MMN, P300) as a means of comparing aging between people with DS and TD individuals, with a view to exploring accelerated aging in DS. For adults with DS, the GFP maximum for MMN decreased with age and MMN latencies increased, which is a typical aging pattern. When comparing aging between the groups (DS, controls), it was found that the younger adults (< 40 years old) were similar whereas older adults with DS (> 40 years old) had a significantly smaller MMN than older controls. The presence of electrophysiological aging in DS, against the absence in age-matched controls, presents a tentative argument that the cortical processes and structures associated with the generation of MMN responses are differentially affected by age in DS.

5 Chapter 5. Examining relationships between EEG measures and neuropsychological measures of executive function

5.1 Aim

To explore whether electroencephalographic measures relate to a range of neuropsychological measures, that have been reported to be sensitive to the functional decline associated with the early stages of Alzheimer's disease in Down's Syndrome.

5.2 Objectives

1. To investigate potential relationships between summary neuropsychological measures and event related potentials (ERPs).

2. To explore whether the ERPs relate to specific neuropsychological measures (scrambled boxes, Tower of London), which are potentially most sensitive to the functional decline associated with the early stages of Alzheimer's disease in Down's Syndrome.

5.3 Introduction

In a prospective, population based study conducted by Ball et al. (2006) it was suggested that early clinical indicators of Alzheimer's disease (AD), for participants with Down's Syndrome (DS), were better defined by changes in personality, behaviour, adaptive functioning and executive dysfunction than by declines in episodic memory. These findings suggest that frontally mediated processes should be the focus when investigating early indicators of AD in DS. Others researchers also subscribe to the hypothesis that AD manifests differently for adults with DS, in the initial stages (Ball et al., 2008; Lott & Head, 2001; Nieuwenhuis-Mark, 2009; Strydom et al., 2010). However, there is some opposition to the proposal that frontal compromise is the first symptom of DS-AD (Blok, Scheirs, & Thijm, 2016; Deb, Hare, & Prior, 2007).

To explore the hypothesis that frontally mediated processes are targeted early in DS-AD, Ball and colleagues developed a battery of assessments for executive function (2006, 2008), appropriate for aging adults with DS (Executive Function test battery for people with Down's Syndrome: EFDS) (Willner et al., 2010). An assessment of the battery found that the number of informant reported changes in personality and behaviour was related to performance on two executive function tasks in the battery: Tower of London (ToL) and scrambled boxes (Ball et al., 2008). In a longitudinal study of 55 adults with DS, informant reported changes in personality and behaviour, at the initial assessment, were significant risk factors for developing the clinical features of Alzheimer's disease, at a five year follow-up (Ball et al., 2006). The most common changes were reduced concern for others and emotional lability (Ball et al., 2006). As the present study is primarily concerned with prospective indicators of AD, the analyses are focused on the tests of executive function (scrambled boxes and ToL), which could be most sensitive to the early signs of AD in people with DS.

The scrambled boxes task was designed to test working memory and response inhibition (Griffith et al., 1999). The task requires participants to remember where the researcher has hidden three coins and inhibit the response to search in the same box. Tower of London (ToL) is a test of planning and working memory (Krikorian et al., 1994). The task is premised on the participant using a set number of moves to match their 'tower' with that of the researcher.

However, executive functioning spans beyond working memory, response inhibition and planning to include activities such as mind-set shifting and self-monitoring (Ball et al., 2008), which are assessed as part of the larger EFDS battery. Furthermore, there are other factors to consider in task performance, such as IQ (as assessed with the KBIT II) and global cognitive function (as assessed with CAMCOG). Therefore, this chapter will firstly examine the relationship between several summary scores of cognitive and intellectual functions, and the ERPs (MMN, P3a, P3b). Then, based on the observations by Ball et al (2008), the relationships between specific cognitive tests of interest (scrambled boxes, ToL) and the ERPs (MMN, P3a, P3b) will be examined.

The ERP measures used in the present study were gained from the global local paradigm: MMN, P3a, P3b. The global local paradigm uses hierarchical predictive coding (Chennu, Noreika, et al., 2013). As discussed in Chapter 3, the MMN response from low-level, attention independent, prediction errors were significantly reduced for participants with DS compared to age- and gender-matched controls. Low-level, attention independent, prediction errors also generated a P3a response. For the participants with DS, the P3a response was significantly enlarged, which could suggest greater distractibility (Fjell & Walhovd, 2004). Furthermore the higher order, attention dependent, prediction errors that generated a P3b response were dramatically reduced, for participants with DS. Based on these findings patterns in chapter 3, one may expect similar results for the lower and higher scorers on the executive function tasks, in the present chapter. Conversely, although the summary neuropsychological measures (CAMCOG-DS, EFDS, KBIT II) have broad clinical utility and therefore warrant investigation; by virtue of being global measures of cognition, these composite scores are unlikely to map onto specific biological processes, such as the ERPs.

5.4 Hypotheses

Hypothesis for objective 1: summary measures

The summary neuropsychological measures (CAMCOG-DS, EFDS, KBIT II) have broad clinical utility, but their breadth also means that they are unlikely to map onto specific ERPs (MMN, P3a, P3b).

Hypothesis for objective 2: specific measures

Participants who score lower on the executive function tasks (scrambled boxes and ToL) will shower smaller field intensities for MMN and P3b, but a larger field intensity for P3a, than higher scoring participants.

5.5 Methods

5.5.1 Exploration of the summary neuropsychological measures

Full details of participant identification; neuropsychological assessments; EEG acquisition; paradigms and pre-processing, can be found in chapter 2, sections 2.5, 2.8, 2.14, 2.15 and 2.16.

The data was pre-processed using custom MATLAB scripts, as described in chapter 2, section 2.16. The GFP maxima were extracted from post-stimulus time frames where the ERPs of interest would be expected: MMN: 100-200ms, P3a: 200-400ms, P3b: 400-650ms. Please see appendix X for the custom script used to gain the GFP values. Please see chapter 3, sections 3.3, 3.7 for more details on the time windows. The GFP maximum and latency values for each ERP time-window (MMN, P3a, P3b), and for each participant, were then exported to SPSS for correlation analyses with the summary, neuropsychological measures: CAMCOG; EFDS Battery; KBIT II.

5.5.2 Exploration of the Tower of London and scrambled boxes tasks

For comparisons between the ERPs (MMN, P3a, P3b) and individual executive functioning tasks of interest (ToL, scrambled boxes), custom MATLAB scripts with SPM utility were used. The data from the executive functioning tasks is ordinal, with a small range. In comparison the EEG data from which the ERPs are derived, is continuous with relatively wide windows of interest. Dichotomies were used in an attempt to manage the disparity in the data types, by creating a clear distinction in task performance. Participants were grouped by their performance on the executive function tasks: lower (<33%), average (33-66%) and higher (>66%) thirds of scorers. The analyses were performed on 16 ‘lower’ scorers and 13 ‘higher’ scorers on the scrambled boxes task, and 15 ‘lower’ scorers and 14 ‘higher’ scorers on the ToL task. The average scorers (7 for scrambled boxes, 7 for ToL) were excluded from the analyses to focus the analyses on the lower and higher scorers, combating the small scoring range, and allowing for clearer answers to the relationship between task performance and electrophysiological factors.

The dichotomy protocol for comparing ‘lower’ and ‘higher’ scorers on the executive function tasks was as follows:

1. makegroups('downs',17) – the number ‘17’ corresponds to subscale (e.g. ToL) being assessed.
2. The output is the participant subject numbers for the ‘lower’ and ‘higher’ scorers on the subscale, which should be copied to the loadsubj. file.
3. spmbatch({'downs_ToL_low','downs_ToL_high'},'EEG') – which includes both aspects of the dichotomy for comparison with the electrophysiological measures (MMN, P3a, P3b).
4. runcon('MMN_dichotomy') – runs the ‘low’ and ‘high’ scorers contrast for each of the electrophysiological measures, a random field theory correction is applied.
5. grandaverage('downs_ToL_high') – generates average waveforms for the group for visualisation at the next step, the grand average should also be run for ‘low’ version of the dichotomy.
6. ploterp('downs_ToL_high',{'ad','ls'},'topowin',[100 200]) – run for each level of the dichotomy and each electrophysiological measure, to allow the potential differences to be visualised.

5.6 Results

5.6.1 Exploration of the summary neuropsychological measures

Objective: To investigate potential relationships between summary neuropsychological measures and event related potentials (ERPs).

Hypothesis: The summary neuropsychological measures (CAMCOG-DS, EFDS, KBIT II) are clinically meaningful measures, which warrant investigation, but their breadth also means that they are unlikely to map onto specific ERPs (MMN, P3a, P3b).

5.6.1.1 Participant demographics

36 adults with DS completed the cross-sectional neuropsychological and EEG testing schedule. Of the 36 adults, 3 had a dementia diagnosis, 21 were male and 33 were right handed. For more demographic details see chapter 3, section 3.5.1. Table 5.1 provides more cognitive detail for the participants.

Variable	Minimum	Maximum	Mean	SD
Age (years)	22	55	37.3	9.39
CAMCOG total score	55	105	83.1	13.7
EFDS total score	12	49	37.5	9.58
KBIT II composite score	40	88	54.6	12.0

Table 5.1. Scores for the summary neuropsychological measures for the cross-sectional phase participants with DS. All the values are rounded to 3.s.f.

5.6.1.2 Whole-group correlations between the summary neuropsychological measures and age

Spearman's Rank-Order correlations (two-tailed) between participants' age and the summary neuropsychological measures found no significant relationships: CAMCOG: $r = .178$, $p = .298$; EFDS: $r = .244$, $p = .152$; KBIT: $r = -.230$, $p = .177$. Therefore, age is considered no further in the following analyses of the summary neuropsychological measures.

5.6.1.3 Whole-group correlations between the summary neuropsychological measures and the ERPs

The Shapiro-Wilk Test of Normality indicated that the GFP maxima and latencies for all the associated ERPs (MMN, P3a, P3b), for the DS group, significantly differed to the normal distribution ($p < .05$). Therefore Non-Parametric, Spearman's Rank-Order correlations were used. To correct for multiple comparisons, the Bonferroni correction is applied at $p < .02$. This level is based on the three ERPs (MMN, P3a, P3b) being clustered in families of GFP maximum (μV^2) and latency (ms): $p < .05/ 3 = 0.02$ (2 d.p.). The investigation is exploratory so the subsequent analyses are two-tailed. All correlations between the summary neuropsychological measures (CAMCOG, EFDS, KBIT II) and the GFP maxima and latencies (MMN, P3a, P3b) failed to reach significance at the $p <.02$ level. The correlation values for each summary neuropsychological measure are displayed in tables 5.2, 5.3, and 5.4. An exploration of each GFP maxima and latency found that either: 1. There were no statistical outliers for the DS or control groups, as no participant was >3 standard deviations from the mean, or 2. If there were outliers, a sensitivity analysis revealed that the results were unchanged by their presence or absence, so they were retained in the analyses. For more details on the results of the sensitivity analysis please see appendix Y.

Summary neuropsych. measures	GFP maxima time-windows (ms)	Associated ERP	GFP Maxima (μV^2)		Latencies of GFP Maxima (ms)	
			r	*p*	*r*	*p*
CAMCOG	100-200	MMN	-.288	.089	.003	.984
	200-400	P3a	-.263	.121	.172	.315
	400-650	P3b	-.008	.963	.161	.347

Table 5.2. Spearman's Rank-Order correlations (two-tailed) between CAMCOG and the GFP maxima and latencies (MMN, P3a, P3b).

Summary neuropsych. measures	GFP maxima time-windows (ms)	Associated ERP	GFP Maxima (μV^2)		Latencies of GFP Maxima (ms)	
			r	*p*	*r*	*p*
EFDS	100-200	MMN	.191	.264	-.019	.911
	200-400	P3a	.048	.780	-.046	.788
	400-650	P3b	-.009	.961	.016	.925

Table 5.3. Spearman's Rank-Order correlations (two-tailed) between EFDS and the GFP maxima and latencies (MMN, P3a, P3b).

Summary neuropsych. measures	GFP maxima time-windows (ms)	Associated ERP	GFP Maxima (μV^2)		Latencies of GFP Maxima (ms)	
			r	*p*	*r*	*p*
KBIT II	100-200	MMN	-.345	.039	.162	.347
	200-400	P3a	-.318	.059	-.014	.937
	400-650	P3b	-.037	.829	.160	.353

Table 5.4. Spearman's Rank-Order correlations (two-tailed) between age standardised KBIT II and the GFP maxima and latencies (MMN, P3a, P3b).

There is an argument that the age standardization of the KBIT II, leads to a high number of adults with DS at floor (Startin et al., 2016). Therefore, the analyses were also run with the raw KBIT scores, which can be found in appendix Z. As with the standardized scores, the raw KBIT II scores also did not correlate with the ERP measures, for the adults with DS. The study also has KBIT II measures for the control participants, a group on which the age standardization procedure was developed. In light of these findings, the thesis continues with the standardized scores.

5.6.2 Exploration of the Tower of London and scrambled boxes tasks

Objective. To explore whether the ERPs distinguish between high and low scorers on specific neuropsychological measures (scrambled boxes, ToL) that are potentially sensitive to the functional decline associated with the early stages of AD in DS.

Hypothesis. Participants who score lower on the executive function tasks (scrambled boxes and ToL) will shower smaller field intensities for MMN and P3b, but a larger field intensity for P3a, than higher scoring participants.

5.6.2.1 Demographics of the dichotomized groups

Independent samples t-tests for Equality of Means were conducted, with Equality of Variances assumed *(p > .05)* to find that the 'lower' scoring and 'higher' scoring groups on the scrambled boxes task did not significantly differ in: age (p = .67), hearing acuity (p = .89), and IQ composite score (p = .43). A chi-square test of independence was performed to examine the relationship between gender (male, female) and group (lower, higher) to find no significant relationship: X^2 (1, 29) = 1.51, p = .219.

Independent samples t-tests for Equality of Means were conducted, with Equality of Variances assumed *(p > .05)* to find that the 'lower' scoring and 'higher' scoring groups on the ToL task did not significantly differ in: age (p = .32), hearing acuity (p = .32), and IQ composite score (p = .46). A chi-square test of independence was performed to examine the relationship between gender (male, female) and group (lower, higher) to find no significant relationship: X^2 (1, 29) = 2.78, p = .096.

The demographics of the groups can be found in tables 5.5 and 5.6.

Group	N	Sex (male)	Mean age (years)	SD	Mean number of tones heard	SD	IQ composite score	SD
Scrambled boxes								
Lower	16	5(11)	37.75	8.72	9.93	1.91	52.31	13.87
Higher	13	7(6)	36.23	10.09	9.85	1.68	56.15	11.32

Table 5.5. Demographics of the groups dichotomized by scrambled boxes score. Sex (male) should be read as: number of females (number of males). Mean number of tones heard indicates the performance on the hearing acuity test. The IQ composite score is gained from the KBIT II. SD refers to the standard deviation of the immediately preceding column.

Group	N	Sex (male)	Mean age (years)	SD	Mean number of tones heard	SD	IQ composite score	SD
Tower of London (ToL)								
Lower	15	5(9)	38.40	7.63	9.47	2.10	53.40	11.53
Higher	14	5(10)	34.86	11.07	10.21	1.84	56.93	13.90

Table 5.6. Demographics of the groups dichotomized by ToL score. Sex (male) should be read as: number of females (number of males). Mean number of tones heard indicates the performance on the hearing acuity test. The IQ composite score is gained from the KBIT II. SD refers to the standard deviation of the immediately preceding column.

5.6.2.2 *Cluster analyses*

The relationship between participants' (DS) performance ('low' vs. 'high') on the executive function tasks (scrambled boxes, ToL task) and field intensity of the ERPs (MMN, P3a, P3b) were explored in SPM. Masks were applied to refine the analysis windows to post-stimulus time frames where the ERPs of interest would be expected: MMN: 100-200ms, P3a: 200-400ms, P3b: 400-650ms (see chapter 3, section 3.3). The SPM images were family wise error (FWE) corrected for multiple comparisons with Random Field Theory (RFT).

The relationship between participants' (DS) performance ('low' vs. 'high') on the scrambled boxes task and the field intensity of P3a was explored in SPM. A mask was applied to refine the analysis window to the time-course where a P3a response would be expected: 200-400ms (post-stimulus). The SPM images were family wise error (FWE) corrected for multiple comparisons with Random Field Theory (RFT). The estimated Gaussian Full Width at Half Maximum (FWHM) smoothness was: 40.2mm x 56.1mm x 55.0ms (9.5 x 10.4 x 13.8 voxels). The RESEL count (R) was 63.24 (2dp):

$R = V / (FWHM_X \times FWHM_Y \times FWHM_Z)$

$R = 86221/(9.5 \times 10.4 \times 13.8)$ (voxels)

$R = 63.24$ (2dp)

Consequently, the statistic images were assessed for cluster-wise significance using a cluster-defining threshold of p <.001 (2.5224e-05). The height threshold (F) was 19.37 (2dp), and the extent threshold (k) was 10 voxels. One cluster was found at this FWE-corrected level (p <.001) of 872 voxels. The cluster has three levels of local maxima (more than 8mm apart). The peak maximum was located 4x 9 x 252 (mm x mm x ms), with an effect size of 31.20 (2dp), at a FWE-corrected p <.05, significance level of p < .001. The maxima details are listed in table 5.7.

N	Maxima of cluster	*x* (mm)	*y* (mm)	*t* (ms)	*Z*	Effect size (*F*)	FWE corrected significance level (*p* <)
872	1.	4	-9	252	5.09	31.20	.001
	2.	-4	2	242	5.04	30.48	.001
	3.	17	2	242	4.23	27.90	.002

Table 5.7. Characterising the cluster in which ‘low’ and ‘high’ scorers on the scrambled boxes differ in P3a global field intensity. N = number of voxels from which the cluster and local maxima are derived. 1-3 = are the local maxima of the cluster, in descending order of strength, 1 is the peak maximum. Location: *x* = ranges from left to right (mm); *y* = ranges from posterior to anterior (mm); *t* = the latency of the ERP (ms). *Z* = Z-score. The FWE corrected significance level of the maxima is also listed (*p* <).

The cluster location is detailed in figure 5.1.

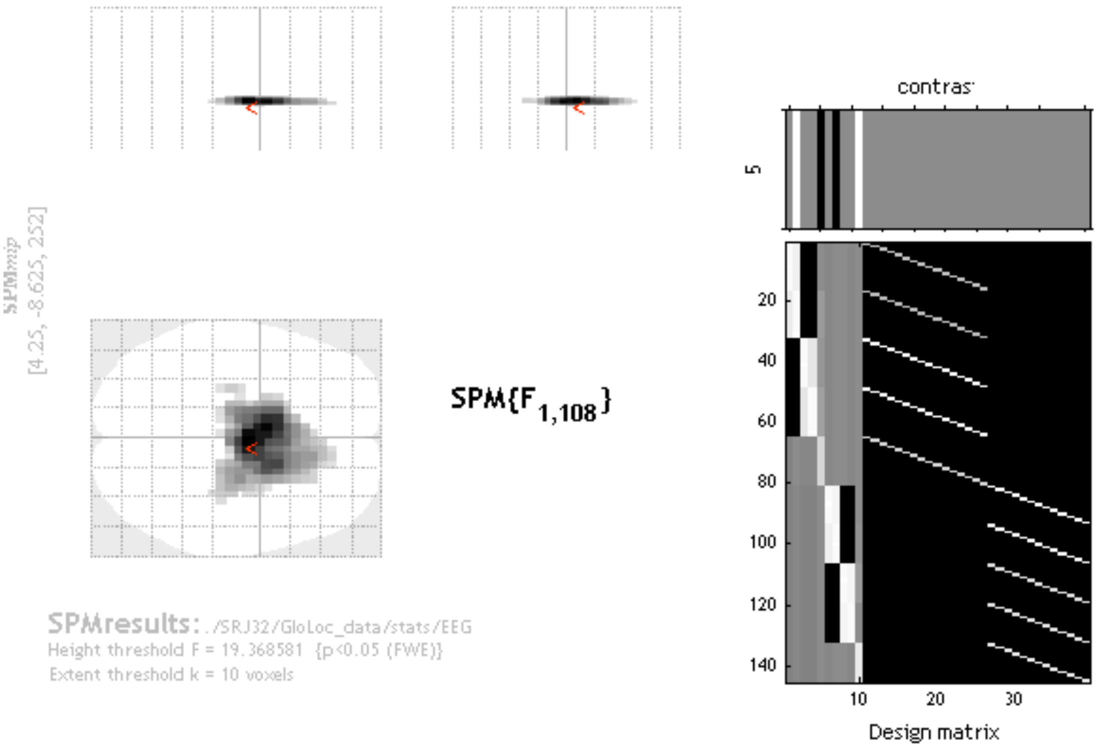

Figure 5.1. The contrasts are calculated for ‘low’ – ‘high’ scoring groups. The contrasts work upon the five experimental conditions: {'ld','ls','gd','gs','ad'},

within the 50-650ms time frame. For the P3a contrast, a 200-400ms mask is used and the contrasts, inline with the conditions, are set up as:[0 1 0 0 -1 0 -1 0 0 1]).

The ‘low’ scorers have a significantly larger P3a field intensity than the ‘high’ scorers, on the scrambled boxes task. This is demonstrated visually in figure 5.2.

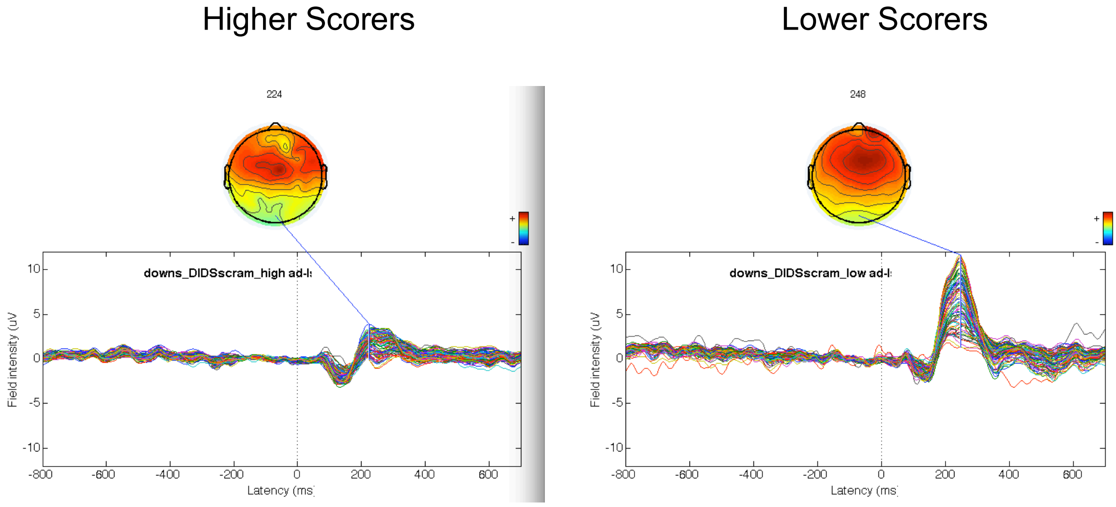

Figure 5.2. Results from scrambled boxes median split dichotomy: left – right, higher scoring group – lower scoring group. Each line maps an individual’s progression over the time course, with 0 indicating the stimulus. There is much higher variability in the lower scoring group. The P3a peak is mapped in the scalp maps. Red indicates positive activity, with blue indicates negative activity. P3a is a positive, fronto-central waveform, as reflected above.

This method was used for all the ERPs (MMN, P3a, P3b) and both executive function tasks of interest (scrambled boxes, ToL) but no more significant clusters were found. The results were as demonstrated in figure 5.3.

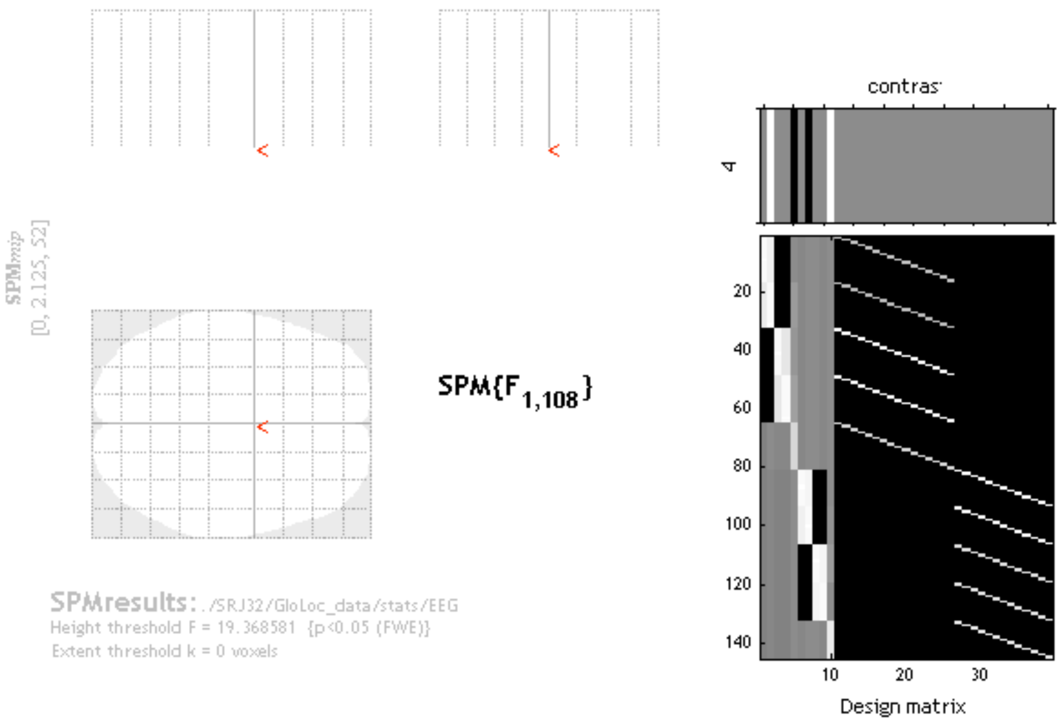

Figure 5.3. The no significant clusters output. This output was seen for all the contrasts between all the ERPs (MMN, P3a, P3b) and executive function tasks of interest (scrambled boxes, ToL), except P3a with scrambled boxes.

5.7 Discussion

The correlational analyses found no relationship between the summary neuropsychological measures (CAMCOG, EFDS, KBIT II) and the ERP measures (MMN, P3a, P3b). This suggests that the subscales, which compose the summary measures either: 1. Do not individually correlate with the ERPs; or 2. Any subscale-ERP correlation effects are diluted by the other subscale non-relationships, when presented as a summary measure. The summary measures are composed of a large number of subscales, which would make individual explorations of all the subscales an insurmountable multiple comparisons problem. Therefore, this finding supports an argument for focusing on the subscales, which are literature-defined as most promising: ToL, scrambled boxes (Ball et al., 2008; Willner et al., 2010).

Although the summary measures were not expected to map onto specific ERPs, the IQ composite measure (KBIT II) moderately correlated with MMN GFP maximum (r = -.345), and may have done so significantly if not for the multiple comparisons correction (p =.039). This correlation was with the IQ composite score, standardised by age, but the same result was found for a correlation with the raw IQ scores: r = -.323, p = .055 (see appendix Z). The summary neuropsychological measures were investigated based on having broad clinical utility, but by virtue of being broad measures they were viewed as unlikely correlates for the specific ERPs. However, in chapter 3 MMN significantly differed for the adults with DS and the TD controls. A key difference between the groups (DS, TD) is their mean IQ; therefore a potential relationship between IQ and MMN is not an unreasonable finding.

In the focused analyses of the executive function tasks (ToL and scrambled boxes), which have been considered most sensitive to the early signs of AD (Ball et al., 2008), performance on the ToL did not significantly correlate with MMN, P3a or P3b responses. The ToL task was developed to assess planning and working memory (Krikorian et al., 1994). Perhaps this did not tie so readily into the electrophysiological (global-local) task demands, which weight more heavily towards learning than planning. However, performance on the scrambled boxes task related to P3a. The ‘lower’ scorers on the scrambled boxes task had a significantly larger P3a field intensity than the ‘higher’ scorers. This pattern mirrors that of the DS (lower scorers) and controls (higher scorers), in chapter 3. This potentially ties into issues with habituating, and inhibiting, a strong response to the rare deviant. The scrambled boxes task was designed to test working memory and response inhibition (Griffith et al., 1999). P3a is a fronto-centrally distributed potential (Polich, 2007), which has been suggested as an index of disinhibition (Fjell & Walhovd, 2004). Executive functions are underpinned by the frontal lobes, the dysfunction of which is implicated in early indicators (Ball et al., 2008; Ball et al., 2010), and relates to potential prognostic indicators (Ball et al., 2006), of AD in DS. Therefore, the results suggest that P3a indexes an executive dysfunction (disinhibition), and relates to a sensitive task (scrambled boxes), implicated in early signs of AD in DS. Of course caution must be taken not to conflate behavioural and sensory inhibition.

An alternative mechanism for the enlarged P3a response seen in DS could be “over-recruitment”. “Over-recruitment” refers to heightened brain responses, which are typically associated with better task performance. However, an fMRI study of typically developing older adults found that those with lower recall task performance had enhanced right PFC dominance (Cabeza et al., 2002). There are three prevailing theories to explain this “over-recruitment’: 1. The lower scoring older adults are inefficiently using the same systems that they have always had, rather than engaging alterative mechanisms (Cabeza et al., 2002); 2. The activity is non-selective, the system has less control (Logan et al., 2002); 3. The more challenging the task the greater the resources, and congruent activity, required to succeed (Grady, 2008). These theories are not mutually exclusive, or directly testable within the framework of the present study. However, it does provide an interesting extrapolation as to why adults with DS who score lower on a neuropsychological measure might display a heightened P3a response.

Of course, any “over-recruitment” model, which relates an enlarged P3a response to executive dysfunction, plays into an ID as well as AD mechanism.

This is an age-old problem of DS-AD research, parsing the ID from the AD (Deb et al., 2007). Indeed, Deb et al. (2007) argues that frontal compromise is a latter symptom in DS-AD but because gaining an AD diagnosis is so difficult in DS, the diagnosis does not occur until this latter stage, thus masquerading as an early clinical symptom. However, for the present study, there were no electrophysiological-neuropsychological relationships with global IQ performance (KBIT II) or global cognitive functioning (CAMCOG), which argues against the P3a-scrambled boxes connection being merely a reflection of global cognitive function, and suggests that there is something specific about the cognitive functions indexed by scrambled boxes task. Furthermore, if one subscribes to a model of early frontal compromise for DS-AD, this relationship could be potentially informative about early stages of the disease.

P300 reflects both the capture (P3a) and maintenance (P3b) of attention. The presence of an enlarged P3a response, in the absence of a significant P3b response, is perhaps unsurprising if you consider the cognitive profile of DS. Implicit memory formation requires the capture but not necessarily the maintenance of attention (Graf & Schacter, 1985), whereas explicit memory formation requires the active maintenance of attentive processes (Graf & Schacter, 1985). In a study by Vicari, Bellucci, and Carlesimo (2000), designed to differentiate the memory types, children with DS had comparable implicit memory performance to TD children but impaired explicit memory performance. Furthermore, information encoding and attention control, which serves explicit memory processes, are significantly impaired in DS (Carlesimo et al., 1997; de Sola et al., 2015). Within a predictive coding framework, the local capture of attention is automatic (P3a) but a failure to encode, contextualize, then retrieve the information at a global level, would lead to a failure in response (P3b).

The enlarged P3a response, in the present study, builds on the frontal shift in P3 seen in previous DS-EEG work (Kakigi et al., 1994; Vieregge et al., 1992). Previous studies have hypothesised that an enlarged frontal P3 (P3a) is a product of: 1. Disturbed P3b generation (Kakigi et al., 1994); 2. Habituation, and inhibition, deficiencies (Díaz & Zurron, 1995b), and 3. A reflection of accelerated aging in DS (Kakigi et al., 1994). The present study addresses each of these hypotheses: 1. P3b generation was disturbed for adults with DS, compared to TD controls (chapter 3); 2. The enhanced P3a correlated with a cognitive measure of inhibition, which would suggest a relationship between the two (chapter 5); 3. The enhanced P3a response did not correlate with age, thus did not reflect accelerated aging (chapter 4). The next step is to explore the clinical value of an enlarged P3a, in terms of its predictive value for cognitive decline (chapter 6).

5.8 Summary

In summary, a neuropsychological assessment (scrambled boxes), which poses congruent demands to the global-local paradigm (learning, attention), most readily mapped onto an electrophysiological product of the paradigm (P3a). A large P3a response for lower scorers on the scrambled boxes task unpicks the large P3a response seen for the DS group in chapter 3. This finding is potentially of clinical interest as the scrambled boxes task is considered one of the most sensitive measures to the early stages of AD in DS. The next step is to assess whether the electrophysiological measures have prognostic value for cognitive decline in DS (chapter 6).

6 Chapter 6. A preliminary exploration of EEG measures as predictors of cognitive decline

6.1 Aim

To investigate the potential value of electroencephalographic (EEG) measures as predictors of cognitive decline in adults with Down's syndrome.

6.2 Objectives

1. To explore the relationship between different modes of imaging (PET, EEG), in the search for early markers of AD in DS.

2. To explore whether the EEG measures (MMN, P3a, P3b) could predict cognitive change, one-year later.

6.3 Introduction

6.3.1 Introductory paragraph

The final stage of the thesis is to explore whether the EEG measures (MMN, P3a, P3b) have prognostic value for the cognitive decline associated with AD in DS. The thesis has built through the chapters. The initial comparison was between people with DS and age-matched controls, which found that people with DS had a significantly smaller MMN, larger P3a, and inconsistent P3b responses. Next, the factor of age was explored to find that MMN was smaller in older adults with DS but not the control group, which is suggestive of accelerated aging. Finally, the relationship with neuropsychological assessments was explored to find that lower performers (with DS) also had a larger P3a response. The predictive value of these ERP measures has been little studied and this thesis only aims for an exploratory analysis. Consequently, the previous findings in the thesis will form a strong basis for the hypotheses in the present chapter.

An investigation into early indicators of AD is important for facilitating early diagnosis and for the evaluation of potential therapeutic interventions. There is great interest in developing markers for preclinical stages of AD so that therapeutic interventions, when they become available, can be administered when there is still functionality to be preserved rather than the more challenging task of restoring lost functions (Jackson & Snyder, 2008).

An exploratory investigation into potential early markers of AD was conducted with two distinct approaches:

1. Multi-modal imaging: PET + EEG (objective 1)
2. Longitudinal follow-up of cognitive data (objective 2)

6.3.2 Introduction to objective 1

A subset of adults with DS also participated in an amyloid imaging study (ethics reference: 11/EE/0348), at a similar time to their EEG and neuropsychological assessments. As part of the amyloid imaging study participants underwent structural and functional MRI scans, as well as a PET scan. We planned an exploratory analysis of this unique, multi-modal dataset because: 1. PET and MRI scans are expensive, and potentially invasive, therefore it would be useful if a less invasive, less expensive technique (such as EEG) could be telling, at least initially, about beta-amyloid (Aβ) load and ease the screening process; and 2. Biomarkers of AD are most likely to be informative in combination (Humpel, 2011), which presents an argument for investigating a combinatory analysis of these modalities.

The multi-modal analysis is specifically focused on the relationship between the EEG and PET scan data. The PET scan images Aβ load with the selective carbon–11 labelled radioisotope PIB (11C–PIB). A comparison of these modalities has been chosen as Aβ accumulation (PET) and synaptic dysfunction (EEG) appear prior to structural brain changes (MRI) (figure 6.1; Sperling et al., 2011). Therefore this small, exploratory analysis is focused on measures, which are sensitive to changes earliest in the AD time course.

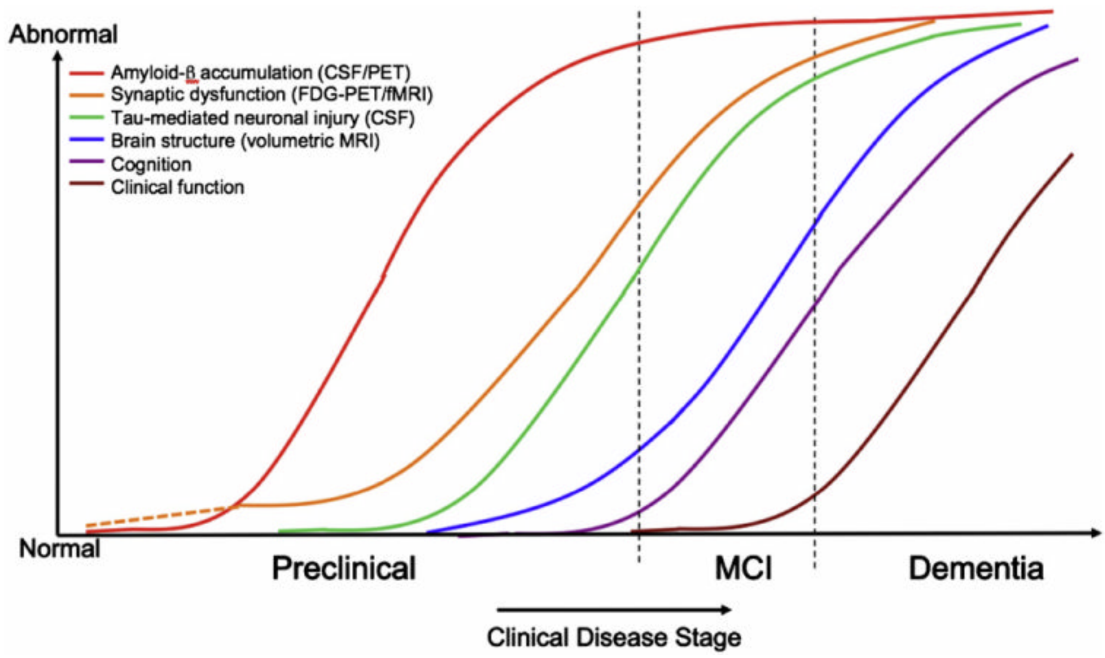

Figure 6.1. "Hypothetical model of dynamic biomarkers of AD" taken from Sperling et al. (2011, pg 21). Aβ accumulation and synaptic dysfunction appear prior to structural brain changes.

Prior to the present amyloid study, which is detailed in Annus et al. (2015), PET imaging with PIB Aβ tracers have been conducted previously with the DS population. The first study was conducted by Landt et al. (2011), which was pilot, proof of concept work. The study found PET imaging to be safe and acceptable for the participants with DS. The ethical considerations of imaging work with potentially vulnerable adults was followed up by d'Abrera, Holland, Landt, Stocks-Gee and Zaman (2013), to confirm these safe and acceptable conclusions. The Landt et al. (2011) study, and the studies which followed (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Sabbagh et al., 2011), agreed a strong age effect with Aβ binding in DS. The studies found that Aβ binding, as indicated by PIB tracers, was generally absent in adults under 35 years old, but consistently present in adults over the age of 45 years. This intimate link with age is a relevant and potential confound for the present study, and AD research more widely.

In terms of investigating the sequence of Aβ binding throughout the DS brain, Handen et al. (2012) was the first to note a striatal beginning to the sequence. Hartley et al. (2014) proceeded to confirm this striatal predominance. The PET work by Annus et al. (2015), which forms the basis of the present analyses, confirmed the striatal finding and described the following sequence of Aβ binding spread, in a cross-sectional sample of adults with DS:

1. Striatum
2. Dorsal prefrontal cortex and anterior cingulate cortex
3. Ventral prefrontal cortex and areas of the parietal lobe
4. Lateral temporal cortex and the rest of the parietal lobe
5. Primary sensory and motor areas
6. Associative visual cortex, premotor cortex, and the rest of the temporal lobe
7. Occipital lobe
8. Thalamus and parahippocampal cortex
9. Amygdala

It is important to reflect on the pattern of Aβ accumulation, to provide biological foundations for the sequence of cognitive compromise in DS-AD.

The comparisons between Aβ binding and cognition were restricted to the CAMDEX (including the CAMCOG-DS) in the Annus et al. (2015) study. The study found that Aβ deposition was associated with lower CAMCOG scores (Annus et al., 2015). The measure was developed by Ball et al., (2006) to be a meaningful assessment of cognitive decline associated with dementia for people with intellectual disabilities (ID). 1. The CAMDEX-DS informant interview takes into account parent/carer's views on changes in the participant's behaviour(s), which may be clinically meaningful. 2. The CAMCOG-DS is a cognitive assessment that is acceptable for people with ID and assesses domains, which may be compromised in AD development. The longitudinal follow-up portion of the present study is also limited to this robust assessment of cognitive decline.

The focus of the present analysis is on the relationship between PIB binding (Aβ load) and the EEG measures (MMN, P3a, P3b). As EEG is a cortical measure the analyses will be restricted to PIB binding in the cortex. P3b was recently explored as a potential AD diagnosis marker for “at risk” older adults (Bennys et al., 2017). The researchers found that P3b latency was significantly increased for the 15 adults who were identified, from PET imaging, as Aβ positive (Bennys et al., 2017). Furthermore, parietal P3b amplitude correctly categorised 69.4% of older adults into the Aβ positive group (Bennys et al., 2017). In light of these findings, we would hypothesise a potential relationship between P3b and PIB binding, in the present study.

The current literature does not compare the other ERPs (MMN,P3a) with PIB binding, so the hypotheses are extrapolated from the findings with this group (DS) from the previous chapters. Firstly, MMN has been shown to be decreased, and latency increased, for older adults with DS (chapter 4), and as age is significantly related to abnormal PIB binding (Annus et al., 2015), a similar pattern may be expected in relation to abnormal PIB binding, in the present study. Secondly, participants with DS have shown larger P3a responses in relation to executive dysfunction (chapter 5). Executive functions are served by the frontal-lobes and are compromised early in DS-AD from both behavioural (Ball, Holland, Treppner, Watson, & Huppert, 2008), and PIB binding (Annus et al., 2015) perspectives. Therefore, we hypothesise that this pattern of an increased P3a may persist in relation to abnormal PIB binding.

Given that markers of AD are most likely to be effective in combination (Humpel, 2011), it will be interesting to consider the interplay between the factors, with an exploratory analysis. Therefore, depending on whether there are independent relationships between the factors (PIB binding, EEG and longitudinal change in CAMCOG score) a combinatory, predictive model of CAMCOG score change will be explored.

6.3.3 Introduction to objective 2

Longitudinal research is essential for identifying accurate predictors of AD. The present study includes an exploratory, longitudinal component in an attempt to ascertain the predictive value of the EEG measures (MMN, P3a, P3b) for cognitive decline. The study was designed with two phases. At the cross-sectional phase, an initial electroencephalographic (MMN, P3a, P3b) assessment and a range of cognitive tests (including CAMDEX-DS) were performed. At the longitudinal phase, approximately one year later, the cognitive assessment that is considered most sensitive to cognitive decline (CAMDEX-DS), was repeated. The CAMDEX-DS includes a cognitive assessment component (CAMCOG-DS) and an informant interview (CAMDEX-DS) (Ball, Holland, Huppert, Treppner, & Dodd, 2006).

The present study assessed cognitive decline as the difference in CAMCOG scores between the cross-sectional and longitudinal phases. The most pertinent guidance for the present study, in the current literature, is a longitudinal cognitive investigation by Benejam et al. (2014). The study used CAMCOG to indicate that adults with DS who transitioned to a dementia diagnosis (within three years) declined by an average of -9.6 points at a one-year follow up (Benejam et al., 2014). Furthermore, the memory, language and visual perception subscales were the primary targets of the decline. People with DS, who did not develop dementia, had a stable total CAMCOG score. However, when creating a dichotomy by age (>/< 40 years), the healthy older adults with DS showed decline on the memory subscale (Benejam et al., 2014).

The present study is primarily concerned with ascertaining the predictive value of MMN, P3a and P3b for cognitive decline. This cognitive decline was assessed by a difference in CAMCOG score after one year. Chapter 5 used CAMCOG to assess global cognitive functioning, at a group level, and from a cross-sectional standpoint. In contrast, the present chapter aims to assess cognitive decline, at an individual level, and from a longitudinal standpoint. The ERPs were selected on the basis that they might be informative about such decline, either by being: 1. A strong correlate (P3b) for AD (Ally et al., 2006), or 2. Informative about frontal mechanisms (P3a), and pathology (MMN; Hughes & Rowe, 2013), which is an early symptom of DS-AD. Nevertheless, again, relationships between the ERPs and cognitive decline are not readily discussed in the DS literature. Therefore the hypotheses are predominantly based on the study findings from previous chapters, and tangible literature sources. 1. P3b is the most robustly associated ERP with AD so it is reasonable to assume that there would be a relationship with CAMCOG change, in a similar fashion of decreasing amplitudes and increasing latencies. 2. The MMN response was clearly decreased, and the latency increased, for older adults with DS (chapter 4); considering that age is intimately linked to cognitive decline and AD development, a similar relationship is expected here. 3. Finally, participants with DS who scored lower on a task of executive dysfunction showed larger P3a responses (chapter 5); considering that executive dysfunction is one of the earliest indicators of cognitive decline associated with dementia (Ball et al., 2008), this pattern may be repeated here.

6.4 Hypotheses

Hypothesis for objective 1: beta-amyloid

Participants with more cortical Aβ are expected to show smaller GFP maxima for MMN and P3b, and longer latencies. Conversely, a larger GFP maximum for P3a is expected.

Hypothesis for objective 2: longitudinal study

The initial GFP maxima for MMN and P3b are expected to be smaller, and the associated latencies longer, for participants who decline on the CAMCOG measure. Conversely, a larger initial GFP maximum for P3a is expected.

6.5 Methods

6.5.1 Design

An initial electroencephalographic (EEG) and cognitive assessment followed, one year later, by a repeat cognitive (CAMCOG) assessment, was the standard study design for all the participants. However, a subset of participants also received beta-amyloid imaging at the initial assessment. The study design is expanded on, by objective, below. A schematic of the study design is detailed in figure 6.2.

Objective 1: 11 participants with DS were enrolled in the amyloid imaging follow-up study (ethics reference: 11/EE/0348), as well as the EEG study. Consequently, these 11 participants had a Positron Emission Tomography (PET) scan within two months of their EEG assessment. The PET scanner used was a GE advance (General Electric Medical Systems, Milwaukee, WI, USA), the data was acquired in 3D mode at Addenbrooke's Hospital, Cambridge. The PET scan lasted 90 minutes and used intravenously administered selective carbon–11 labelled radioisotope PIB (11C–PIB) to image the Aβ. Mr Liam Wilson and Dr Tiina Annus, from the Cambridge Intellectual and Developmental Disabilities Group, University of Cambridge, collected and analysed the PET data. Dr Annus defined the ROIs for PIB analysis by manually improving the Brodmann atlas in Colin27 space, collapsing across smaller Brodmann regions. The details of the PET scan and analysis details can be found in Dr Annus' paper (Annus et al., 2015). Dr Young T. Hong and Dr Tim D. Fryer at the WBIC, University of Cambridge, conducted the kinetic modelling and reconstruction of PET data. As EEG is a cortical measure the focus of the comparative PET analyses were on the 'Added Brodmann' values, which reflect a global cortical region of interest (ROI).

The amyloid study used the same neuropsychological assessments as the EEG study. The amyloid study also involved a 45 minutes MRI scan at Addenbrooke's Hopsital, using a three Tesla Siemens Verio scanner

(Siemens AG, Erlangen, Germany). The focus of the analyses remains on comparisons between the EEG, neuropsychological and PET data.

Objective 2: 35 participants with DS who completed the initial EEG assessment (MMN, P3a, P3b), which includes the 11 with a PET scan, were re-approached 10-14 months later (mean 12 months) for a follow-up cognitive assessment with the participant (CAMCOG), and informant-interview with the parent or carer (CAMDEX). The analyses are focused on the difference between participants' CAMCOG scores at the cross-sectional phase (Time 1) and the longitudinal phase (Time 2). The total CAMCOG difference score is the score at Time 2 minus the score at Time 1 (T2-T1).

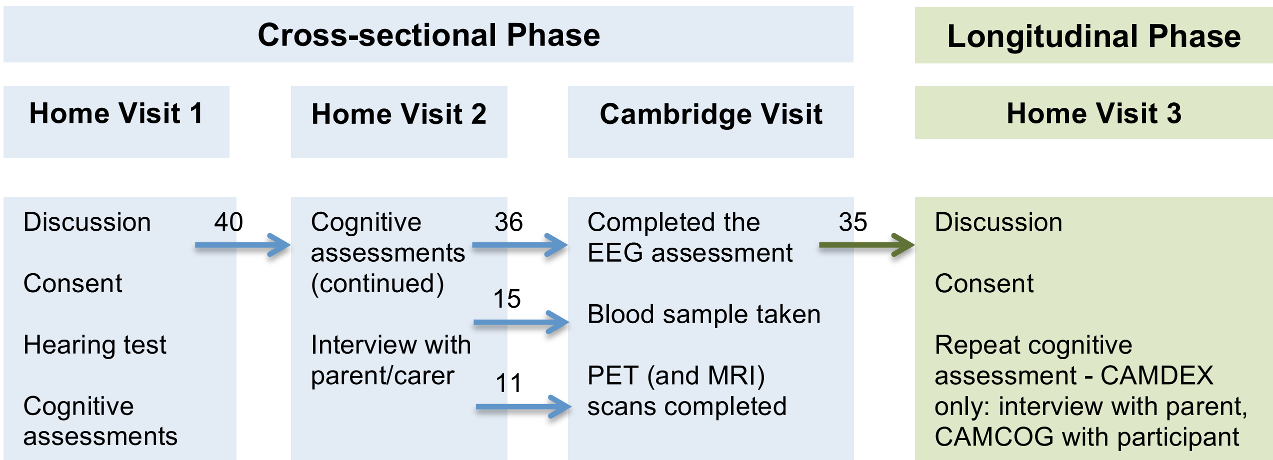

Figure 6.2. A schematic of the study design: left to right is the chronological order of the study, the blue sections are cross-sectional, and the green are longitudinal. The numbered arrows denote the number of participants who transitioned from one phase of the project to the next. The numbered arrows from 'Home Visit 2' to 'Cambridge Visit' indicate that 36 participants completed the EEG assessment, of which 15 successfully had blood samples taken and 11 had PET (and MRI) scans. 35 of these participants transitioned to the 'Longitudinal Phase'.

6.6 Results for objective 1

Objective 1. To explore the relationship between different modes of imaging (PET, EEG), in the search for early markers of AD in DS.

Hypothesis for objective 1. Participants with more cortical Aβ are expected to show smaller GFP maxima for MMN and P3b, and longer latencies. Conversely, a larger GFP maximum for P3a is expected.

6.6.1 Demographics for the amyloid imaging study participants

11 adults with DS participated in the amyloid imaging study and had a PET scan at a similar time to their EEG assessment. Of the 11 adults, 3 had a dementia diagnosis, 7 were male and 10 were right handed. Table 6.1 provides more demographic and cognitive detail.

Variable	Minimum	Maximum	Mean	SD
T1 Age (years)	37	52	45.4	4.94
T1 KBIT IQ composite score	40	75	59.6	9.64
T1 total CAMCOG score	65	101	86.6	11
T2 total CAMCOG score	48	101	83.1	15.3
T2-T1 total CAMCOG score	-17	3	-3.45	6.31

Table 6.1. Demographics for the participants who took part in the EEG study and amyloid imaging study. T1 = time 1 (initial assessment), T2 = time 2 (follow-up assessment). SD = standard deviation from the mean. The values are rounded to 3 significant figures (s.f.).

As EEG is a cortical measure the focus of the comparative PET analyses were on the 'Added Brodmann' values, which reflect a global cortical region of interest (ROI). Aβ is visualized in a PET scan when bound to 11C–PIB, which generates PIB binding values. Table 6.2. provides details of participants' PIB binding values, figure 6.3. visualizes the values.

Age	Gender	Added Brodmann
37	F	-0.022230067
39	M	0.036087267
43	F	0.159041754
45	M	0.016788009
45	M	0.399464693
47	M	-0.008080844
47	M	0.067498316
47	F	-0.006233943
51	M	0.422107944
52	F	0.016097132
53	M	0.689384281

Table 6.2. The PIB binding scores for the participants, ranked in ascending order by participant age.

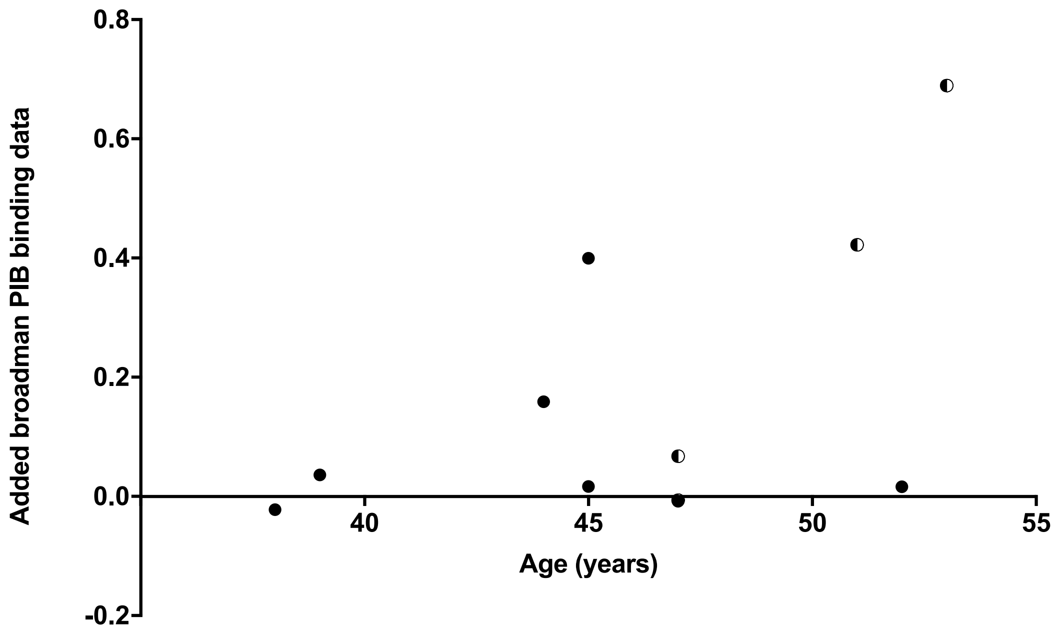

Figure 6.3. The PIB binding scores for the participants, ranked in ascending order by age. The half black and white dots are participants with DS-AD.

6.6.2 Correlations between cortical beta-amyloid load and EEG

The PIB binding values of the 11 participants for the global cortical ROI ranged from -.02 to .69 with a mean of .16 (*SD* = .24). Spearman's Rank-Order correlations were used to compare the global cortical ROI PIB binding values to the EEG measures (MMN, P3a, P3b). To correct for multiple comparisons, the Bonferroni correction was applied at $p < .02$ (=.05/3). No significant correlations were found at this level. The results of the correlations are shown in table 6.3.

PIB binding values for the global cortical ROI	GFP maxima time-windows (ms)	Associated ERP	GFP Maxima (μV^2)		Latencies of GFP Maxima (ms)	
			r	*p*	*r*	*p*
	100-200	MMN	-.445	.170	.396	.265
	200-400	P3a	.264	.433	-.303	.365
	400-650	P3b	-.382	.247	-.382	.247

Table 6.3. Spearman's Rank-Order correlations (two-tailed), between the PIB binding values for the global cortical ROI and ERPs (MMN, P3a, P3b); all values are rounded to 3 s.f.; the significance level is set at $p < .02$.

Spearman's Rank-Order correlations (two-tailed) to compare the global cortical ROI PIB binding values to the EEG measures (MMN, P3a, P3b), found a correlation coefficient (*r*-value) between MMN and PIB binding of -.445. However, this relationship was not significant ($p > .02$) with the tested sample size of 11 adults with DS. However, a correlation coefficient of -.445, within a two-tailed test, and Bonferroni corrected significance level of $p <.02$, would be expected from a sample size of 47 (Hulley, Cummings, Browner, Grady, & Newman, 2013).

6.6.3 Correlations between cortical beta-amyloid load and total CAMCOG difference scores (T2-T1)

A Spearman's Rank-Order correlation (two-tailed), between the PIB binding values for the global cortical ROI (M = .16, SD = .24) and total CAMCOG difference (T2-T1) score (M = -3.45, SD = 6.31), found no significant relationship ($r = -.229$, $p = .497$). As cortical Aβ load did not correlate with the total CAMCOG difference score it is not an appropriate entry into a combinatory (with EEG) model of the variable.

6.7 Results for objective 2

Objective 2. To explore whether the EEG measures (MMN, P3a, P3b) could predict cognitive change, one-year later.

Hypothesis for objective 2. The initial GFP maxima for MMN and P3b are expected to be smaller, and the associated latencies longer, for participants who decline on the CAMCOG measure. Conversely, a larger initial GFP maximum for P3a is expected.

6.7.1 Review of participant data

Initially 35 of the participants with DS were followed up. On reviewing the researcher's notes for all of the CAMCOG tests (T1 and T2), it was found that one participant (29 year old male), at T1, had fulfilled criteria for "uncooperative behavior", "silly behavior" and "flat affect". Additional notes from the researcher included: "gave up far too fast, just answering no or I don't know to a lot of the questions." There were no such notes on their follow-up test (T2). The differing states-of-mind of the participant most likely explains the vastly improved test-score (+16) between the two time points. The study is concerned with cognitive changes rather than changes in mood, presenting grounds for excluding the participant. The following analyses are focused on the remaining 34 participants.

6.7.2 Participant demographics for the follow-up study

34 adults with DS completed initial (cognitive + EEG) and follow-up (cognitive only) assessments. Of the 34 adults, 3 had a dementia diagnosis at T1, 20 were male and 32 were right handed. No participants transitioned to an AD diagnosis between T1 and T2. Table 6.4. provides more demographic and cognitive detail for the participants. Figure 6.4 is a graph of each participants' cognitive results (CAMCOG total score) at the initial (time 1) and follow-up assessments (time 2). Figure 6.5 depicts the spread and distribution of the group's time 1 and time 2 CAMCOG scores.

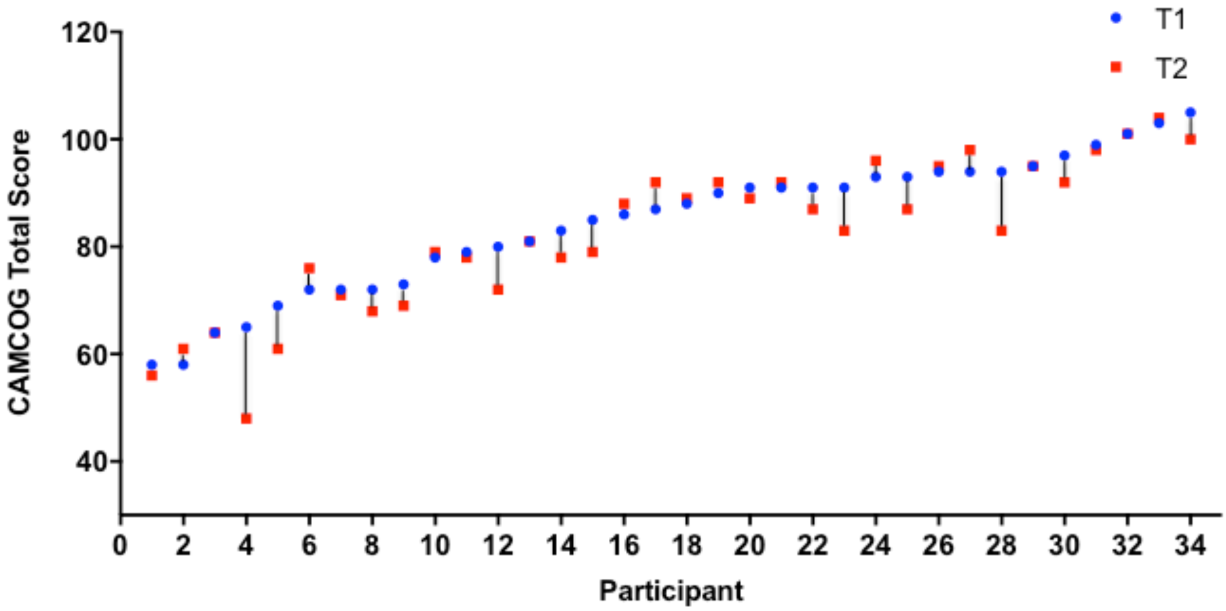

Figure 6.4. Graph of each participant's total CAMCOG score at time 1 (T1: blue circle) and 2 (T2: red square). The vertical line between the points shows each participant's change in total CAMCOG score between time 1 and 2. Participants' are ranked in ascending order by their total CAMCOG score at time 1.

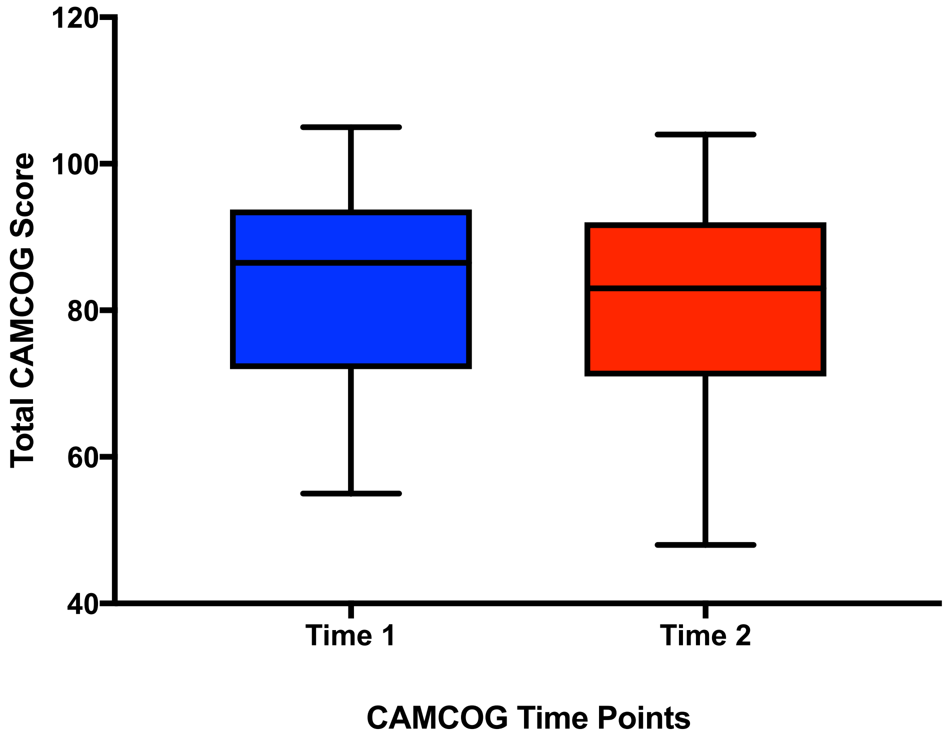

Figure 6.5. Boxplots of the participants' with DS total CAMCOG scores at time 1 and time 2, 10-14 months later.

Variable	Minimum	Maximum	Mean	SD
T1 Age (years)	22	55	37.6	9.42
T1 KBIT IQ composite score	40	88	55	12
T1 total CAMCOG score	58	105	83.9	13
T2 total CAMCOG score	48	104	82.4	14
T2-T1 total CAMCOG score	-17	5	-2.06	4.77

Table 6.4. Demographics of the longitudinal phase participants. T1 = time 1 (initial assessment), T2 = time 2 (follow-up assessment). SD = standard deviation from the mean. The values are rounded to 3 s.f.

6.7.3 Correlation between total CAMCOG difference scores and age

A Spearman's Rank-Order correlation (two-tailed) between participants' total CAMCOG difference score (T2-T1) and age found no significant relationship: $r = -.102$, $p = .561$. Therefore, age is considered no further in the following analyses of CAMCOG difference scores (T2-T1).

6.7.4 Correlations between total CAMCOG difference scores and T1 EEG

The Shapiro-Wilk Test of Normality indicated that the GFP maxima and latencies for all the associated ERPs (MMN, P3a, P3b), for the adults with DS, significantly differed to the normal distribution ($p < .05$). Therefore Non-Parametric, Spearman's Rank-Order correlations were used. To correct for multiple comparisons, the Bonferroni correction was applied at $p < .02$. This level was based on the three ERPs (MMN, P3a, P3b) being clustered in families of GFP maxima (μV^2) and latency (ms): $p < .05/ 3 = .02$ (2 d.p.). The investigation is exploratory so the subsequent analyses are two-tailed.

The 34 participants' total CAMCOG difference score ranged from -17 to 5 points with a mean change of -2.06 points (*SD* = 4.77 points). For participants with DS, the GFP maximum within 100-200ms (MMN) positively correlated with participants' total CAMCOG difference score (T2-T1 performance): r = .506, p = .002. The relationship is displayed in figure 6.6. All other correlations between the total CAMCOG difference score and the GFP maxima (P3a, P3b) and latencies (MMN, P3a, P3b) failed to reach significance at the p <.02 level. The correlation values are displayed in table 6.5.

Total CAMCOG difference score (T2-T1)	GFP maxima time-windows (ms)	Associated ERP	GFP Maxima (μV^2)		Latencies of GFP Maxima (ms)	
			r	*p*	*r*	*p*
	100-200	MMN	.506*	.002	-.007	.969
	200-400	P3a	.063	.723	-.036	.838
	400-650	P3b	-.092	.603	.270	.123

Table 6.5. Spearman's Rank-Order correlations (two-tailed), between total CAMCOG difference scores (T2-T1) and ERPs (MMN, P3a, P3b); all values are rounded to 3 s.f.; * indicates correlations which are significant at p < .02 level; T1 = (time 1) the initial cognitive test visit; T2 = (time 2), the follow-up visit 10-14 months after T1.

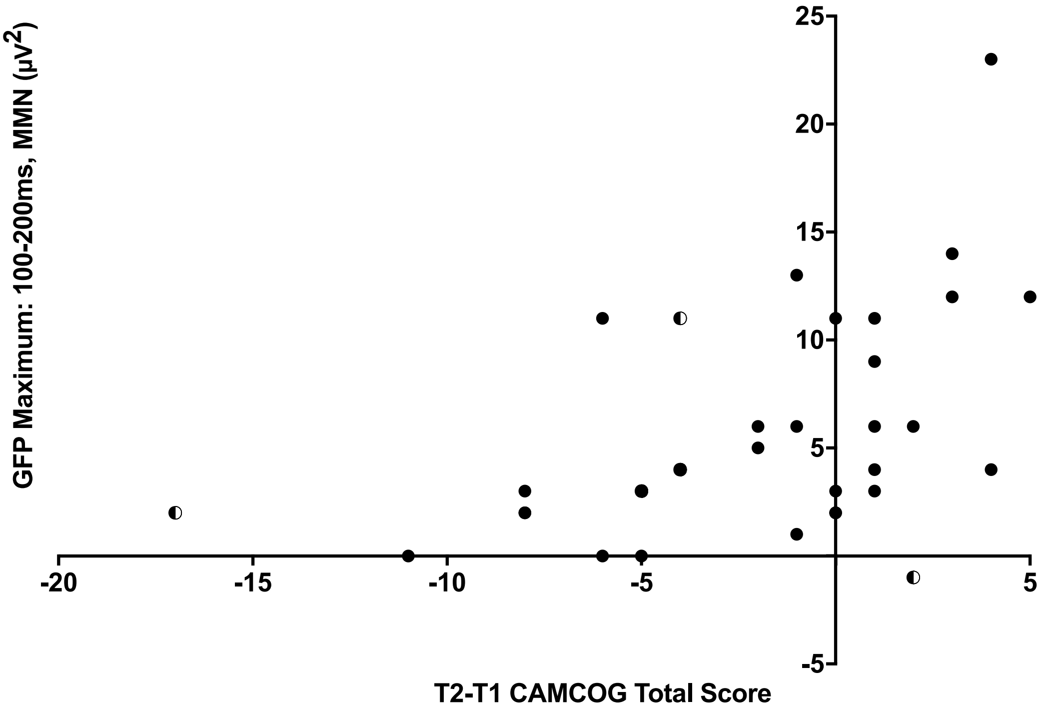

Figure 6.6. The relationship between cognitive difference scores (=T2-T1 total CAMCOG score) and mean GFP maxima (MMN). The half black and white dots are participants with DS-AD. One adult with DS-AD has shown a rapid decline in their total CAMCOG score, which, considering their diagnosis is perhaps unsurprising.

6.7.5 Correlations between CAMCOG subscale difference scores and T1 MMN

To further explore the relationship between MMN GFP maxima and the total CAMCOG difference score, the seven separate subscales: orientation, language, memory, attention, praxis, perception, and abstract thinking were correlated with the MMN GFP maxima, using Spearman's Rank-Order. For participants with DS, the GFP maximum within 100-200ms (MMN) positively correlated with participants' total CAMCOG difference score (T2-T1 performance) on the praxis task: $r = .447$, $p = .008$. The relationship is displayed in figure 6.7. All other correlations between the subscales and MMN GFP maxima failed to reach significance ($p > .05$). The results of the correlations are shown in table 6.6.

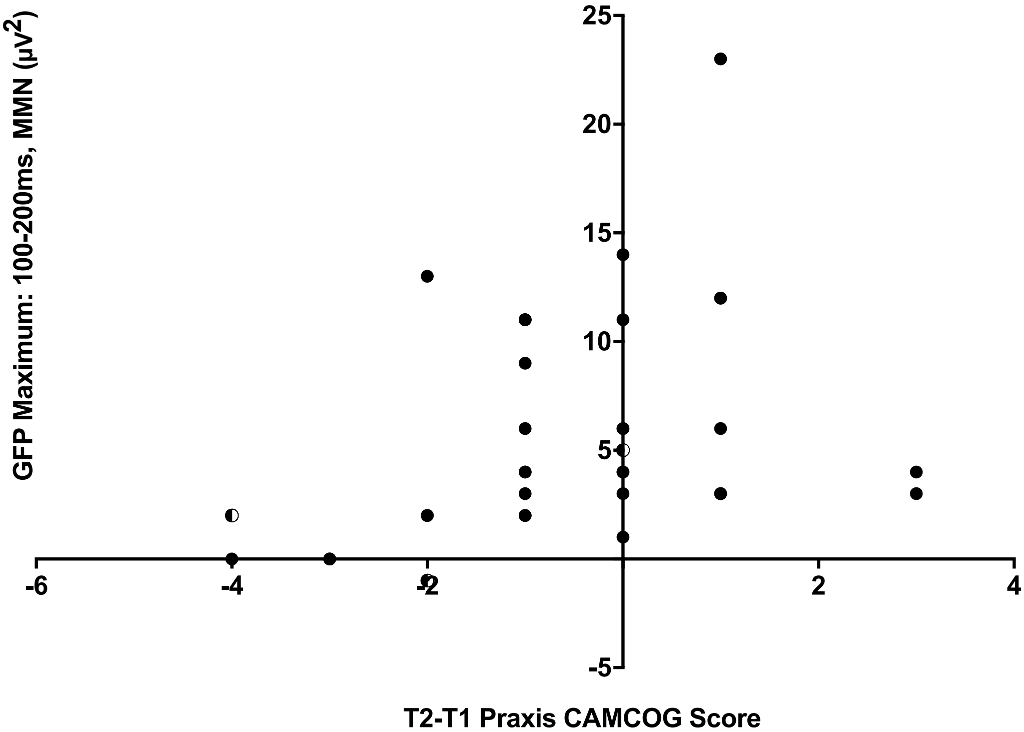

Figure 6.7. The relationship between praxis changes from T1 to T2 (=T2-T1 praxis CAMCOG score) and Mean GFP maxima (MMN). The half black and white dots are participants diagnosed with DS-AD.

CAMCOG subscale difference scores (T2-T1)			Correlations with the MMN GFP Maxima (100-200ms)	
Subscale	*M*	*SD*	*r*	*p*
Orientation	-.03	1.29	.088	.622
Language	.06	2.71	.184	.297
Memory	.11	2.91	.268	.125
Attention	-.23	1.11	.084	.636
Praxis	**-.57**	**1.61**	**.447***	**.008**
Perception	.43	1.15	-.005	.976
Abstract Thinking	-1.17	2.38	-.115	.516

Table 6.6. Spearman's Rank-Order correlations (two-tailed) between the difference scores (T2-T1) on the CAMCOG subscales (orientation, language, memory, attention, praxis, perception, and abstract thinking) and participants' MMN GFP Maxima. All the values are rounded to 3 s.f.; *significant at $p < .01$; T1 = (time 1) the initial cognitive test visit; T2 = (time 2), the follow-up visit 10 14 months after T1; M = mean CAMCOG subscale difference score; SD = standard deviation of the mean CAMCOG subscale difference score.

6.8 Discussion

6.8.1 Key findings

An exploratory investigation into potential electrophysiological predictors of the cognitive decline associated with AD development (in DS), was conducted with two distinct approaches:

1. Multi-modal imaging: PET + EEG (objective 1)
2. Longitudinal follow-up of cognitive data (objective 2)

The key findings from the approaches were as follows:

Objective 1. Cortical beta-amyloid load correlated with neither the EEG measures (MMN, P3a, P3b), nor cognitive change after one year (T2-T1 CAMCOG score). As a result, a predictive, combinatory (EEG + PET) model of cognitive difference scores was not explored.

Objective 2. Participants' initial MMN correlated with the difference in total cognitive functioning, and praxis, a year later. The difference scores were calculated by subtracting participants' CAMCOG performance at initial testing from their performance a year later (T2-T1 CAMCOG scores). All other correlations between cognitive difference and the EEG measures (P3a, P3b) failed to reach significance.

6.9 General discussion

A relationship between Aβ load and cognitive decline may have been expected as Annus et al. (2015) found a relationship between CAMCOG scores and PIB binding with a similar cohort of DS participants. However, the Annus et al. (2015) comparison was made with cross-sectional CAMCOG scores rather than longitudinal change. Furthermore, due to the exploratory nature of the present study, the sample was limited to 11 participants, which is much less than the 49 participants with DS tested in the Annus et al. (2015)

study. The present study was also restricted to PIB binding in the cortex rather than exploring the whole brain.

A cortical ROI for PIB binding was used, as EEG is a cortical measure. A whole cortical ROI was used, rather than fractioning by region because: 1. The poor spatial resolution of EEG makes localization difficult. 2. With adult aging there can be topographical shifts of ERP sources, for example MMN may present more parietally with increasing age (Anderer, Semlitsch, & Saletu, 1996). 3. The morphology of the DS brain is fundamentally different to that of the typically developing population with: reduced overall cortical volume (Lott, 2010); disproportionately diminished frontal lobes (Aylward et al., 1999); reduced neuronal density (Lott, 2010), amongst other features. Therefore, for an inclusive approach, which attempts to avoid these potential confounds, the whole cortex was analysed rather than fractioning by region. Moderate and medium effect sizes were shown for the relationships between the ERPs and PIB binding (see table 6.2.), although the relationships failed to reach significance (p >.02). Furthermore, post-hoc sample size calculations revealed that a sample of 47 participants with DS would have been expected to find a correlation coefficient of r = -.445 (MMN comparison with PIB), at the p < .02 significance level. Therefore, although no significant relationship was found between the PIB and EEG data in the present study of 11 participants, this finding should be tempered by the exploratory, and inherently underpowered, nature of the comparison.

The focus of the present analysis is on cognitive change rather than raw cognitive performance because: 1. Lower CAMCOG scores at T1 did not predict lower CAMCOC scores at T2 (see figure 6.4.) and 2. Cross-sectional CAMCOG performance did not correlate with the ERP measures (see chapter 5).

The relationship between MMN and total change in CAMCOG score suggested that participants with smaller MMN were most likely to show the largest declines in CAMCOG score, after one year. Indeed, a visual inspection of the data (see figure 6.5) suggested that the 4 participants who dropped more than 7 points over the course of the year drove the correlation between MMN and CAMCOG change. Previous work has suggested that adults with DS who transition to a dementia diagnosis (within three years) have the largest declines in CAMCOG score: an average of -9.6 points at a one-year follow up (Benejam et al, 2014). Therefore, if the largest declines in CAMCOG score have the strongest relationship with MMN, then this EEG measure may be applicable for predicting AD development. This hypothesis could be tested in future work with longer follow-up periods, in which time there is an increased chance of greater decline rates (>7 points), and transitions to an AD diagnosis.

The CAMCOG subscales were investigated to unpick the relationship with the total score. The exploratory analysis found a relationship between MMN and praxis change. A smaller MMN, at the initial assessment, predicted a decline in praxis performance a year later. The praxis subscale is used to assess the voluntary motor functions of drawing and performing actions to command (Ball, Holland, Huppert, Treppner, & Dodd, 2006). As part of the subscale, participants are asked to copy drawings of varying difficulty: circle, square, house and clock (Ball et al., 2006). Participants are also asked to demonstrate how they would perform actions, such as waving and cutting with scissors (Ball et al., 2006). The enaction of these skills requires planning and voluntary motor selection, which are functions served by the associative striatum (Jankowski, Scheef, Hüppe, & Boecker, 2009). The associative striatum encompasses the precommisural putamen and caudate nucleus, of the dorsal striatum, which receive projections from the frontal and prefrontal cortices (Afifi, 2003; Jarbo & Verstynen, 2015). With the biological underpinnings of praxis in mind it is interesting to consider the typical pattern of Aβ accumulation as people with DS age: beginning at the striatum then moving to the frontal lobes (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014). The early vulnerability of areas involved in praxis to Aβ accumulation suggests that performance on this subscale might be informative about early cognitive compromise in DS-AD.

There are complexities and limitations of the study design, which will be briefly discussed here and more extensively tackled in chapter 7. Due to the time-constraints of PhD, the follow-up was limited to one year later, and only contained a cognitive component. This feeds into the challenges of dementia research more generally: the protracted nature of AD versus the narrow sampling window that is feasible within a research context. Furthermore, the sample is small, and the number of participants who declined significantly over the course of the year, smaller still. However, the results suggest that MMN may have potential for predicting cognitive decline in adults with DS, as indexed by the CAMCOG assessment. How MMN fairs as a potential biomarker against the criteria set out by Humpel (2011) will be addressed in the general discussion (chapter 7).

6.10 Summary

The overarching aim of this thesis has been to investigate the potential value of EEG measures as predictors of cognitive decline. The chapters have built on one another in an effort to achieve this over-arching aim: Firstly, establishing a baseline of how adults with DS differ from typically developing individuals on the measures used; secondly, exploring the premature aging hypothesis in DS; thirdly, looking at the relationship between the electrophysiological and neuropsychological, focusing on executive dysfunction as one of the first markers of AD in DS; finally, moving from markers to predictors, exploring EEG predictors of cognitive decline in DS. The general discussion (chapter 7) will use the information gathered in these chapters to evaluate EEG as a biomarker of AD, within the context of DS research.

7 Chapter 7. Discussion

7.1 Thesis aims

The overall thesis aims were addressed in each of the findings chapters:

1. To use electroencephalographic measures (MMN, P3a, Pb) to compare adults with Down's Syndrome and typically developing controls, within a predictive coding framework (*chapter 3*).

2. To use electroencephalographic measures as a means of testing the accelerated brain aging hypothesis in Down's Syndrome (*chapter 4*).

3. To explore whether electroencephalographic measures relate to a range of neuropsychological measures, that have been reported to be sensitive to the functional decline associated with the early stages of Alzheimer's disease in Down's Syndrome (*chapter 5*).

4. To investigate the potential value of electroencephalographic measures as predictors of cognitive decline in adults with Down's syndrome (*chapter 6*).

7.2 Study outline

The over-arching aim of the thesis has been to investigate the potential value of EEG measures as predictors of cognitive decline. A high-density EEG array net was used to acquire EEG data on MMN, P3a and P3b, from 36 adults with Down's Syndrome (DS) and 39 age- and gender-matched typically developing (TD) controls. The EEG data was analysed in three ways in an attempt to achieve the over-arching aim. Firstly, the extent to which the EEG measures differ, but are comparable, between adults with DS and TD adults was established. Secondly, the EEG measures were used to explore the premature neurological aging hypothesis of DS. Thirdly, the cross-sectional relationship between the electrophysiological and neuropsychological measures was established: the focus being on neuropsychological measures of executive dysfunction, which is one of the first markers of Alzheimer's disease (AD) in DS. With these findings, finally, the thesis transitioned from markers to predictors, by exploring EEG as potential predictors of cognitive decline. The main limitations of the study include the potential confounds of intellectual disability and age; the generalizability of the research beyond the sample; and the practical challenges of performing all of the required measures and recruiting adults with DS-AD.

7.3 Abstract of main findings

This thesis initially compared adults with DS to TD controls, to find that the participants with DS had significantly: smaller MMN, larger P3a, and inconsistent P3b responses. Next, the factor of age was explored to find that MMN was smaller in older adults with DS but not the control group, which is suggestive of accelerated aging. Then, the relationship with neuropsychological assessments was explored to find that lower performers (with DS) also had a larger P3a response. Finally, the prognostic value for cognitive decline was explored to find a relationship between MMN and total cognitive change, and praxis changes.

7.3.1 The relationships between the findings

- Adults with DS showed a large P3a response in chapter 3. The lower scorers on an executive functioning task showed the same enlarged P3a response in chapter 5.
- MMN showed a relationship with advancing age in chapter 4, and predicting cognitive decline in chapter 6.

7.4 Summaries of the main thesis findings, within the context of the literature

7.4.1 Using EEG measures to compare adults with Down's Syndrome to typically developing controls

The thesis began by establishing a baseline of how the ERPs of interest (MMN, P3a, P3b) appear for adults with DS, compared to age- and gender-matched TD controls. The purpose of the initial comparison was to confirm that although the ERPs are likely to differ quantitively between groups, they do not differ qualitatively. This chapter was a chance to confirm and update the limited ERP data for adults with DS, and establish a time-window of interest for a novel form of ERP measurement, with this group: global field power (GFP).

In line with previous research, participants with DS showed significantly smaller MMN (Arisi et al., 2012; César et al., 2010; Lalo et al., 2005), and P3b (Blackwood et al., 1988; César, Caovilla, Munhoz, & Ganança, 2010; Kakigi, Neshige, Matsuda, & Kuroda, 1994; Lalo, Vercueil, Bougerol, Jouk, & Debû, 2005; Medaglini et al., 1997; Seidl et al., 1997; St. Clair & Blackwood, 2013; Vieregge, Verleger, Schulze-Rava, & Kömpf, 1992; Wetter & Murphy, 1999) responses, than TD controls.

This chapter also showed that whilst the controls showed a standard P3b response, the adults with DS showed a very large P3a response. This finding could be tied into a relationship between the cognitive profile of DS and the differing attentional demands of the P300. Attention control and encoding are particularly impaired in DS (de Sola et al., 2015), meaning that attention can be captured (enlarged P3a), but not necessarily maintained and encoded (no P3b).

Having established the waveforms at a group level, the following chapters go on to explore the effects of: age (chapter 4), executive dysfunction (chapter 5), and cognitive decline (chapter 6).

7.4.2 *The accelerated aging hypothesis of Down's Syndrome*

This chapter used the ERP measures (MMN, P3a, P3b) as a means of comparing aging between adults with DS and TD individuals, with a view to exploring accelerated neurological aging in DS. As would be expected from ERP-aging research with the TD population (Alain, McDonald, Ostroff, & Schneider, 2004; Alain & Woods, 1999; Bertoli, Smurzynski, & Probst, 2002, 2005; Cooper, Todd, McGill, & Michie, 2006; Czigler, Csibra, & Csontos, 1992; Horváth, Czigler, Birkás, Winkler, & Gervai, 2009; Horváth, Czigler, Winkler, & Teder-Sälejärvi, 2007; Karayanidis et al., 1995; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Pekkonen et al., 1996; Pekkonen, 2000; Rimmele, Sussman, Keitel, Jacobsen, & Schröger, 2012; Schiff et al., 2008; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015; Woods, 1992), for the adults with DS the MMN decreased with age and the latency increased.

However, there was no age effect on the ERPs for controls, which could be a product of youth. Previous aging research with TD controls classed older adults as 60+ years (Tsolaki et al., 2015). In contrast, the present study classed older adults as 40+ years because this is a critical age for adults with DS in terms of when abnormal beta-amyloid (Aβ) binding begins (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Sabbagh et al., 2011). Indeed, a comparison based on this dichotomy found that the younger adults (< 40 years old) were similar across groups (DS, controls); whereas older adults with DS (< 40 years old) had a significantly smaller MMN than older controls.

The relationship between age and MMN in DS, against an absence for age-matched TD controls, presents a tentative argument that the cortical processes, and structures, which generate MMN show accelerated aging in DS.

7.4.3 Executive dysfunction in Down's Syndrome

The summary cognitive measures (CAMCOG, EFDS, KBIT II) are useful clinically but, as expected, reflect a wide range of functions that do not readily map onto specific electrophysiological processes (MMN, P3a, P3b). However, a neuropsychological assessment (scrambled boxes) which is considered to be sensitive to the early behavioural changes seen in DS-AD (Ball et al., 2008), was related to an electrophysiological component (P3a). Indeed, the enlarged P3a response seen in the DS-controls comparison was unpicked by this neuropsychological-electrophysiological relationship. Adults who scored lower on the scrambled boxes task showed significantly larger P3a field intensities than higher scorers. These components (scrambled boxes, P3a) both tie into inhibitory mechanisms (Fjell & Walhovd, 2004; Griffith et al., 1999). However, care must be taken not to conflate behavioural (scrambled boxes) and sensory (P3a) inhibition.

An alternative mechanism for the enlarged P3a response seen in DS could be "over-recruitment": heightened activity. There are three prevailing theories for an over-recruitment model of the enlarged P3a response in lower scoring adults with DS: 1. Systems are being used inefficiently, and there is a failure to engage new pathways (Cabeza et al., 2002); 2. The systems are being engaged in an inefficient and uncontrolled manner (Logan et al., 2002); 3. The task is more challenging for lower scoring participants, therefore more resources, and congruent activity, are required (Grady, 2008). Although these theories cannot be directly tested within the framework of the present study, they provide an interesting extrapolation for future work.

Having established a cross-sectional relationship between electrophysiological (P3a) and neuropsychological (scrambled boxes) measures; the next step was a longitudinal exploration of the electrophysiological measures as prognostic indicators for cognitive decline in DS.

7.4.4 Cognitive decline in Down's Syndrome

The overarching aim of this thesis has been to investigate the potential value of EEG measures as predictors of cognitive decline. Chapter 6 employed two approaches in an attempt to achieve this aim: exploring the relationship between different modes of imaging (EEG, PET) and, assessing whether EEG measures (MMN, P3a, P3b) could predict cognitive change (T2-T1 CAMCOG), one year later.

The cortical Aβ load, gleaned from the PET scans, correlated with neither the EEG measures, nor cognitive change after one year. However, how Aβ accumulates in the DS brain is of interest considering that an EEG measure (MMN) predicted decline on praxis. For older adults (40+ years) with DS, Aβ begins by accumulating in the striatum before moving to the frontal lobes (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014), and these fronto-striatal circuits serve the motor function of praxis.

A global cognitive change (T2-T1 CAMCOG total score), after one year, was predicted for participants with a smaller MMN at the initial assessment. Indeed, an inspection of the data found that participants with the largest drops in score (> 7 points) predominantly drove the relationship between MMN and CAMCOG change. This observation is of interest considering that a longitudinal, cohort study of 44 adults with DS found that those adults (10) who developed dementia showed an accelerated rate of change to their CAMCOG scores, averaging at -9.6 points after the first year (Benejam et al., 2014). In the present thesis, no participants made the transition to dementia. This limitation leaves it to future work to assess whether cognitive decline, predicted by lower MMN and indexed by CAMCOG change, is indicative of AD development in DS.

7.5 Evaluation of EEG against biomarker criteria

The definition of a 'biomarker' is: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention" (Biomarkers Definitions Working Group., 2001). This thesis has focused on evaluating electroencephalography (EEG) as measure of the typical biological process of aging, and as a potential indicator for the pathological development of AD in DS.

'Criteria for establishing a good biomarker for the diagnosis of dementia' have been set out previously by Humpel (2011, p. 27, box 1). However, the criteria set out by Humpel (2011) were focused on evaluating blood and cerebral spinal fluid biomarkers. Therefore, the present project used a refined and categorised version of the criteria so potential electroencephalographic markers of AD could be evaluated. Please see table 7.1, for the refined criteria and how the present, and future, EEG work can be evaluated against it.

Categories	Criteria for establishing a good biomarker for the diagnosis of dementia	Criteria for **present** EEG project	Criteria to consider in **future** EEG work
Sensitive and specific	Reflect physiological aging processes	✓	✓
	Reflect cognitive measures of AD	✓	✓
	Display high sensitivity to AD, independent of aging effects	✓	✓
	Display high specificity for AD, compared with related disorders	×	✓
Feasible	Should be measurable in non-invasive, easy-to-perform tests	✓	✓
	Should not cause harm to the individuals being assessed	✓	✓
	Tests should be inexpensive and rapid	✓	✓
	Easy collection of data, not only in hospitals	✓	✓
	Data should be relatively simple and inexpensive to analyse	✓	✓
	Allow measurements repeatedly over time	✓	✓
Scientifically robust	Allow reproducibility in laboratories worldwide	✓	✓
	Changes should be at least two-fold to allow differentiation from controls	×	✓
	Define good cut-off values to distinguish diseases	×	✓
	Data published in peer-reviewed journals	×	✓
	React upon pharmacological intervention	×	✓

Table 7.1. Criteria for evaluating EEG as a marker of AD for the present project and future investigations. Adapted from 'criteria for establishing a good biomarker for the diagnosis of dementia' by Humpel (2011, p. 27, box 1).

From this exploratory study, MMN seems to be the most promising candidate for indicating cognitive decline, as measured by the CAMCOG. Indeed, the ERP measure is related to both cognitive decline and age (Chapter 4), as independent variables, which satisfies much of the "sensitivity" criteria for a good biomarker. Furthermore, the inexpensive and non-invasive nature of EEG technology satisfies the "feasibility" criteria. The key issue with the study's evaluation of potential EEG markers is the focus on cognitive decline rather than a specific sensitivity to the diagnostic development of AD. Unsurprisingly, as the cognitive follow-up was only one year after the initial assessment, no one transitioned to a dementia diagnosis, which inevitably limited the analysis to cognitive decline rather than diagnostic transition. The study is a small-scale, preliminary exploration of ERPs as markers for cognitive decline. Consequently, although the technology is widely available for reproducing the results in other laboratories, the work has yet to be conducted. Therefore it remains for future work to satisfy the “scientifically robust” criteria. The findings suggest that EEG markers are potentially feasible and sensitive to cognitive decline. Future explorations with larger cohorts, followed over longer periods of time, will tell if the markers retain feasibility in terms of scientific rigour, sensitivity and specificity to AD.

7.6 Considerations, challenges and limitations

7.6.1 Potential confounds

The thesis confounds are largely discussed in terms of the common comorbidities with AD: ID, age, and epilepsy. An AD diagnosis is inherently difficult to make for adults with DS (Deb et al., 2007; Nieuwenhuis-Mark, 2009; Strydom et al., 2010; Zeilinger et al., 2013), largely due to difficulties in parsing the associated ID with the development of dementia symptoms (Sheehan et al., 2015). Furthermore, the approaches taken to making a dementia diagnosis in DS are numerous, and inconsistent, across studies (Nieuwenhuis-Mark, 2009). Nevertheless, Nieuwenhuis-Mark (2009) does recommend the semi-structured informant interview: CAMDEX-DS (Ball, Holland, Huppert, Treppner, & Dodd, 2006), which was used to diagnose dementia in the present study. However, an informant interview is inherently a reflection of the parent/carer’s view of the participant’s functioning, which is frequently slanted towards changes which are most obvious and have the largest impact on the informant’s life (Nieuwenhuis-Mark, 2009).

The ID associated with DS can not only confound a dementia diagnosis (Sheehan et al., 2015), but interact with symptomology development. In relation to the EEG findings of the present thesis, the stereotypical difficulty with maintaining attention in DS is a key, confounding, cognitive deficit. P3b is contingent on the active maintenance of attention, which is a difficult activity for adults with DS (de Sola et al., 2015; Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). Given this cognitive deficiency, it is perhaps unsurprising that issues with attention maintenance were reflected in difficulties in generating a consistent P3b response. P3b is the most consistently used potential for investigating AD in the TD population (Ally, Jones, Cole, & Budson, 2006). In the present thesis, the unreliable P3b result may be a reflection of how the pre-morbid DS cognitive phenotype interacted with EEG development. P3b may thus be an inappropriate measure for investigating the development of DS-AD. From a further cognitive standpoint, subjective memory complaints are a significant AD symptom, which are also affected by attention difficulties (Dubois et al., 2014). These findings present the argument for longitudinal investigations of DS-AD: comparisons with participants' own baselines rather than cross-sectional comparisons between individuals. This thesis has made an exploratory attempt at this research method with a longitudinal, cognitive follow-up after one year, to investigate the relationship with participants' initial EEG findings.

There is debate as to whether AD development is related to a critical "age" range, or is an inevitable part of the "aging" process (Ritchie & Kildea, 1995). Nevertheless, there is an intimate and irrefutable link between age and AD. As a consequence, controlling for age effects can also control for AD effects. As the EEG data was not normally distributed, the present thesis attempted to tackle age effects, when age effects were not the primary outcome measure, by assessing whether there was an independent effect on the variable of interest, with a series of Spearman's Rank-Order correlations. For example, both age (chapter 4) and cognitive decline score (chapter 6) correlate with MMN but they do not correlate with one another (chapter 6). Therefore, the assumption is that the effects of the variables on MMN are independent. Please see figure 7.1 for a visualisation. The system is by no means perfect, but does make logical and meaningful assumptions from the non-parametric data.

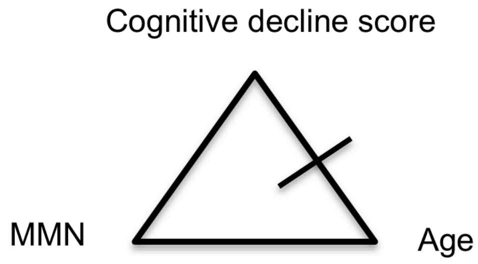

Figure 7.1. Schematic for how cognitive decline and age both correlate with MMN, but not one another, therefore we can assume that their relationships with the variable (MMN) are independent.

Late-onset epilepsy is a common occurrence for adults with DS-AD (Evenhuis et al., 1990; Lai et al., 1989; Mendez & Lim, 2003). This thesis is concerned with using EEG measures to research cognitive decline, and EEG measures are typically used in epilepsy clinics; therefore, epilepsy is a relevant and potential confound to this work. Due to timing and staffing, a neurophysiologist did not examine the EEG recordings. However, none of the participants had an epilepsy diagnosis. Furthermore, only three participants had a DS-AD diagnosis, and this is the group that would be at highest risk for late-onset epilepsy.

As only three participants had a DS-AD diagnosis, their data was considered in the homogenous, DS group analyses. This decision was made because: three is too small a group for independent analyses; the removal of the three both detracts from the overall sample size and fails to acknowledge the contributions from these participants. Furthermore, considering the difficulties of diagnosing AD in DS (Deb et al., 2007; Nieuwenhuis-Mark, 2009; Strydom et al., 2010; Zeilinger et al., 2013), combined with the inevitability of AD pathology in this group (Ball et al., 2006; Holland et al., 1998; Mann, 1988, 2006), all of the participants could be considered to be on a spectrum of deterioration. Where participants met criteria for a dementia diagnosis, based on the ICD-10 and a psychiatrist's review of the CAMDEX-DS, they have been highlighted in visualisations of the data. The performance of adults with

DS-AD do not cluster, instead they were disparate, leading us to believe that they were not skewing the findings, but instead add to the power of the study.

7.6.2 Generalisability

As one of the primary concerns of the research was investigating premature aging in adults with DS, care was taken to recruit approximately 10 adults per decade (20s, 30s, 40s, 50s) in both the DS and TD control groups. The groups were also matched for gender. Nevertheless, it is acknowledged that these adults are a self-selecting group for research, which may not necessarily be representative of the population.

For the adults with DS, the average life expectancy is 57.8 years old for women and 61.1 years old for men, in developed countries (Bittles et al., 2007; Glasson et al., 2003). Consequently, the study is inherently limited to an investigation of aging, up to the 50s, and this is for both groups (DS, controls), as they were age-matched. For the present study, the effect of age on MMN was limited to the adults with DS. The thesis has discussed this finding as a reflection of accelerated aging as the adults with DS are reaching this MMN reduction first. Previous research with TD controls has found an age effect with MMN when older adults were considered to be 60+ years (Tsolaki et al., 2015). Therefore, more confidence in the premature aging hypothesis could be found by adding an older control group.

Another product of the reduced life-expectancy in DS (Bittles et al., 2007; Glasson et al., 2003), is preferential sampling. The recruitment of adults in their 50s was particularly difficult, especially because there are high rates of AD pathology in this age-range (Mann, 2006). Adults with co-morbid DS-AD were less likely to be recruited because they are considered a more vulnerable group, and are more likely to be supported by carers rather than parents. The care homes that were prepared to engage with and support research were included in the study whereas those that were not remain an unknown quantity. Every effort was made to engage with care homes, and the large demands on carers' time that research requires, from reimbursing the care home for the carers' time to organising taxis to pick up and drop off participants, from local homes. Nevertheless, it was particularly difficult to engage adults with DS-AD, potentially because of the misconceptions around "research". Furthermore, none of the participants transitioned to a dementia diagnosis over the course of the longitudinal study. As a result, the thesis is limited to an investigation of cognitive decline rather than predicting AD development.

For the controls, every effort was made to generate a representative sample by using 'Join dementia research' (JDR), which is a national database. The JDR control participant search criteria quickly gained female participants within 15 miles of Cambridge. However, males were particularly difficult to recruit, resulting in the search radius increasing to 50 miles of Cambridge. The large search radius had the advantage of capturing participants outside of the 'Cambridge bubble', in an attempt to generate a potentially more representative IQ range.

7.6.3 Practical challenges

AD is a protracted disease from which a PhD research project necessitates studying a narrow sampling window. Consequently, although the thesis has included a longitudinal component, the follow-up is only after one year, which limits the focus of the thesis to cognitive change rather than AD development.

The modality of stimuli delivery when eliciting ERPs was an important consideration in the context of DS because problems with vision and to a lesser extent hearing are frequently reported in this population (Lott, 2010). Consequently, the ERPs were elicited in the auditory domain as auditory compliance is easier to maintain than visual (Bekinschtein et al., 2009). To identify potential hearing problems, participants' hearing was screened at the home visit and the tones were played during testing at a level that was considered comfortable for each participant.

For the global-local paradigm, striking the balance between what was achievable for adults with ID, yet still engaging enough for TD controls, was a challenge. The global effect (P3b) is premised on participants actively engaging with the task, which typically requires participants to count groups of sounds (Bekinschtein et al., 2009). Nevertheless, the global effect has been observed in some minimally conscious adults, meaning that the verbal recall of group numbers is not necessary to generate the effect (Bekinschtein et al., 2009). In the present study, participants were asked to describe the **groups** of sounds**,** rather than the more demanding task of both identifying the groups, and counting them. The TD controls were able to focus on the task and generated a robust P3b effect. However, most adults with DS struggled to maintain their attention on the task and move beyond the verbal recall of rare, deviant sounds. Consequently, the adults with DS showed a large, attention capture, P3a response but failed to show attention maintenance with a consistent P3b response. This finding suggests that although the paradigm is very effective for generating attention independent responses in DS (MMN, P3a), it may not be appropriate for generating an attention contingent response (P3b).

The perceived difficulty of the task can influence the nature of the P300 response (Polich, 2007). For easier tasks there are more parietal, P3b influences in the response; whereas harder tasks elicit more frontal, P3a responses (Polich, 2007). In this way, the perceived difficulty of the task can present issues in generating a consistent P300 effect. This difficulty distinction was reflected in the findings: a P3a dominated response for adults with DS, and a P3b response for the control participants (chapter 3). As the groups were so heterogeneous in ability it was very difficult to match both within- and between- groups in terms of difficulty, whilst still maintaining a comparable paradigm. The present study chose to use the same paradigm for all participants, in the interests of parity at a stimulus level. Future work could attempt to distinguish the effects of perceived difficulty by using a paradigm in which perceptual difficulty is gradually, and sequentially, increased. A study of this type would accommodate individuals' ability levels, whilst still providing some directly comparable data in which the same stimuli are tested with both groups.

From a practical standpoint, it was extremely difficult to gain blood samples from the adults with DS, which meant that consequent blood analyses, such as ApoE status, could not meaningfully be performed. A research nurse who was trained in phlebotomy took the blood samples for the present study. However, future work may consider recruiting a phlebotomist who specialises in difficult cases.

During the EEG analyses the researcher was blind to the participant's identity, however the group to which they belonged (DS, controls) was discernible. A participant's group was recognisable based on their identification number: controls < 40. Furthermore, the DS EEG data was significantly noisier than the control data. Therefore, even if the identification numbers had been randomised, it would still have been obvious during pre-processing (step 4) which group an individual belonged to. Nevertheless, this lack of blinding leaves the study potentially vulnerable to unknowing bias by the researcher. In contrast, the follow up study was undertaken blind to each participant's initial EEG result.

7.7 Future directions

7.7.1 Developing the research

Based on the limitations and challenges of the present work, the key improvement to the study would be the addition, or expansion, of the following groups: older controls, DS-AD, generalised ID, and abnormal Aβ binding.

For a more comprehensive review of aging, a larger age range of participants is required. Recruiting older adults with DS is challenging due to life-expectancy restrictions, which has recently been reported at between 50 (Coppus, 2013) and 60 years old (Glasson et al., 2003). However, a cohort of older adults (60+ years) from the typically developing population would provide more certainty to the claims that aging in DS is premature, as measured by ERPs, and that control participants will eventually demonstrate a similar progression.

Due to recruitment difficulties, the present thesis only included three adults with DS who also have a diagnosis of AD. Consequently, in order to meaningfully include these adults in the analysis, their data has been collapsed into the DS group and their presence highlighted, as appropriate, on the graphs. The ultimate aim of the research is to assess whether the ERPs are useful predictors of AD development. As nobody developed AD over the course of the present study, the present study is limited to an exploration of cognitive decline (as measured by CAMCOG), which may, or may not, be indicative of AD development. AD is a protracted illness, and the present study only takes a small snapshot of adults with DS progression on that trajectory. As always with AD research, the only way to truly track the progression towards the disease is to take a larger sampling window. The present study includes a one-year follow-up with some promising results; repeated cognitive follow-ups at five-year intervals would be an excellent addition.

As always with DS-AD research there is the issue of disentangling the cognitive compromise due to the ID, from the development of AD. For this reason, longitudinal work is of particular importance with this group in order to focus on individual change rather than cross-sectional performance. As chapter 3 displayed, the ERPs (MMN, P3a, P3b) are quantitatively different between adults with DS and TD controls. It was beyond the time constraints of the present study, but the addition of a group of IQ matched adults with ID, but without a DS diagnosis, would be of interest when trying to parse ID from AD symptoms, and their effect on electrophysiology.

A combination of biomarkers will likely provide the most accurate representation of whether adults will develop AD (Humpel, 2011). As a result, it would be of interest to analyse across a larger multi-modal imaging set (EEG, PET, MRI – structural, functional). The present thesis made an attempt at multi-modal analysis but with only 11 participants the investigation was limited.

To truly expand the work, studies need to be able to acknowledge that AD does not develop ‘cleanly’. For example, epilepsy is closely linked with DS-AD (Evenhuis et al., 1990; Lai et al., 1989), EEG is typically used for epilepsy research, and so this could be an interesting extension.

7.7.2 Future analyses for the acquired data

One potential future analysis avenue for the MMN data acquired in this study is dynamic causal modelling (DCM). DCM can be used to create a plausible, dynamic representation of EEG responses (David, Harrison, & Friston, 2005; Friston, 2003). Specifically, DCM can be used to explain ERPs as a network of interacting cortical sources (David et al., 2005). Indeed, Garrido, Kilner, Kiebel, and Friston (2007) used DCM to explain MMN as an interaction of forward, backward and lateral connections between the primary auditory cortex, superior temporal gyrus and inferior temporal gyrus. The study was concerned with testing hierarchical predictive coding, and whether MMN was driven by forward connections, backward connections, or both (Garrido et al., 2007). DCM tests specific models, driven by the literature, rather than being a wide-spread exploratory technique (Garrido et al., 2007). For this reason, although DCM can also be applied to resting state data it is often more powerful when tied to a specific, well-defined response. The long history of MMN research, combined with its consistently reliable production (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001), makes it an ideal paradigm with which to test DCM. Having used DCM, on an MMN paradigm, to explore hierarchical predictive coding in TD adults (Garrido et al., 2007), the model could now be extended to adults with DS. This extension would potentially be informative about the mechanisms, which underlie MMN generation in DS.

7.7.3 Future EEG paradigms to consider

This section discusses EEG paradigms that future work could use to explore the interaction between DS, typical and pathological (AD) aging.

7.7.3.1 Resting state EEG

The acquisition of resting-state EEG data requires only limited cooperation from participants and is therefore an appropriate tool irrespective of participants' cognitive abilities. EEG data gathered under a resting-state, passive paradigm can be analysed in several ways. The analyses described here are an indicative, rather than exhaustive, list of the potential methods for interpreting resting-state EEG data.

EEG spectral analyses have been used previously to indicate a slowing and reduction of faster frequencies (alpha, beta) and increase of slower frequencies (theta, delta) in people with AD compared to age-matched controls (Bennys, Rondouin, Vergnes, & Touchon, 2001). Coherence analyses are performed on EEG data to approximate the functional connectivity between different areas of the cortex (Jeong, 2004). Coherence analyses calculated on EEG data from people with AD have indicated decreased coherence of alpha and beta bands, suggesting reduced functional connectivity (Dunkin, Leuchter, Newton, & Cook, 1994). Furthermore EEG data has excellent temporal resolution, making it an ideal basis for investigating physiological complexity in the brain (Catarino, Churches, Andrade, Baron-Cohen, & Ring, 2011). As a promising candidate, the next section will elaborate on physiological complexity.

Physiological complexity in the brain describes the interactive nature of the system, for example by feedback loops, over multiple time- and spatial-scales (Goldberger, Peng, & Lipsitz, 2002). Multi-scale entropy (MSE) is a coarse-graining procedure which quantifies the complexity of physiological signals by comparing sample entropies across multiple time-scales (Costa, Goldberger, & Peng, 2002). MSE analyses can be performed upon 60 second artefact-free epochs of resting state EEG data (Mizuno et al., 2010). A study conducted by Takahashi et al. (2009) investigated EEG complexity and aging with MSE to show that older adults (mean age 64.5 years old) had reduced EEG signal complexity compared to younger adults (mean age 29.2 years old). Furthermore, previous studies have successfully used MSE to disambiguate people with AD (but not DS) from age-matched controls (Escudero, Abásolo, Hornero, Espino, & López, 2006; Jeong, 2004; Mizuno et al., 2010; Park, Kim, Kim, & Kim, 2007). The studies predominantly found that EEG data gathered from people with AD were less complex over multiple timescales than age-matched controls, which suggests a significant reduction in non-linear dynamics (Escudero et al., 2006; Jeong, 2004; Park et al., 2007). The ease of data acquisition, combined with the promising results from aging and AD groups, suggest that it would be feasible to evaluate MSE as a potential index of aging and AD, in DS.

7.7.3.2 Electrophysiological measures of 'gating' for investigating DS-AD: P50 suppression and acoustic startle prepulse inhibition

The filtering of redundant sensory information by the central nervous system is called 'gating' (Adler et al., 1982). 'Gating' can be either: 1. 'Sensory', which refers to a suppressed response from cortical neurons; or 2. 'Sensorimotor', which refers to a suppressed muscular response (Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004). 'Sensory gating' is typically assessed by the attenuated magnitude of an ERP response to the second in a pair of repeated clicks, under the P50 Suppression paradigm. 'Sensorimotor gating' is typically assessed by the attenuated magnitude of an electromyography (EMG) response to a startling auditory stimulus, which follows a weak tone, under the prepulse inhibition (PPI) paradigm. The P50 Suppresion and PPI paradigms will now be further discussed with reference to their potential utility for investigating aging and early indicators of AD, in DS.

P50 is an early, positive evoked potential elicited 40-70ms after an auditory stimulus (Thomas et al., 2010). The auditory stimulus usually used to evoke P50 is a 50ms 'click', played in a passive 'dual-click paradigm' with a silent movie distracter task. The ‘dual-click paradigm’ is when the same ‘click’ is presented twice, with an inter-stimulus interval of 500ms and inter-trial interval of 8-10s, resulting in P50 suppression (Adler et al., 1982). P50 suppression is the diminished response (reduced P50 amplitude) to the second ‘click’ of the pair compared to the first because of the ‘sensory gating mechanism’(Thomas et al., 2010). The ‘sensory gating mechanism’ is the inhibition of irrelevant (repeated) information which results in reduced neural activity to that stimulus so cognitive processing is focused on potentially more useful (novel) information (Bender et al., 2014). P50 reduces in amplitude with age whereas P50 suppression is relatively robust to aging effects but is diminished in AD (Thomas et al., 2010). P50 suppression could be reduced in AD compared to age-matched controls because the echoic memory trace of the first stimulus decays too rapidly to be sufficiently available to instil a suppression effect by the time it’s pair is played (Bender et al., 2014). This hypothesis reflects the memory deficits which characterise typical AD; however the neuropsychological correlates of P50 suppression are of more interest for AD-DS symptomatology. The neuropsychological correlates of P50 suppression are predominantly executive functions (including working memory requiring inhibition and attention) which are underpinned by the frontal lobes (Thomas et al., 2010). This is of particular interest in the context of AD-DS because, as previously discussed, the earliest clinical indicators are best defined by changes in personality, behaviour and executive dysfunction (Ball et al., 2006). Furthermore, reduced sensory gating for people with AD correlating with worse performance on neuropsychological tests of working memory requiring inhibition (Thomas et al., 2010) is of particular interest as Ball, Holland, Watson and Huppert (2010) found behavioural disinhibition to be one of the earliest and most frequently reported signs of AD in DS.

‘Sensorimotor gating’ is when the motor response to sensory stimulation is involuntarily reduced (Ueki, Goto, Sato, Iso, & Morita, 2006). Acoustic startle prepulse inhibition (PPI) is an experimental manipulation used to measure ‘sensorimotor gating’. The PPI paradigm plays a weak auditory stimulus (prepulse) approximately 120ms before a startling auditory stimulus (pulse) to inhibit the reflexive startle response of an eye blink (Ueki et al., 2006). The reduced eye blink response is measured by applying two electrodes to the skin which overlays the orbicularis oculi muscle (Blumenthal et al., 2005). The electrodes then conduct the eye blink EMG signal to the recording equipment, which can be the same equipment used in EEG and ERP experiments (Blumenthal et al., 2005). Physiologically, the inhibition of the startle response occurs in the pons but is regulated by the limbic cortico-striato-pallido-pontine circuitry (Swerdlow et al., 2001). The cortico-striato-pallido-pontine circuitry includes a fronto-striatal loop. PPI as an electrophysiological reflection of fronto-striatal loop functioning is of interest considering recent PET imaging studies have indicated striatal dominant PiB binding in people with DS without AD (Annus et al., 2015; Handen et al., 2012; Hartley et al., 2014).

The PPI paradigm has been used with typically developing individuals, demonstrating that it is greatest for middle-aged individuals but the startle eye blink reflex is significantly decreased in amplitude and increased in latency for older adults (Ellwanger, Geyer, & Braff, 2003). Previous experiments have failed to find that PPI disambiguates AD from typical aging (Hejl, Glenthøj, Mackeprang, Hemmingsen, & Waldemar, 2004; Ueki et al., 2006). However, PPI could be informative about early indicators of DS-AD if: 1. People with DS are preferentially accumulating Aβ in the striatum; 2. Aβ in the striatum disrupts fronto-striatal loops; 3. The disruption of fronto-striatal loops compromises frontal lobe functioning; 4. Changes to cognitive functions underpinned by the frontal lobes characterise the early stages of DS-AD, as the Ball et al. (2006, 2008) studies suggest.

7.7.4 Future drug trials

The true value of EEG work in DS-AD research is what it can tell you mechanistically, and using this information to guide future treatment trials. For example, MMN is mediated by glutaminergic mechanisms (Javitt, Steinschneider, Schroeder, & Arezzo, 1996), and this information can be used in terms of current and future drug trials.

Memantine is non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which was originally developed by Eli Lilly in 1968 to combat diabetes. The Food and Drug Administration (FDA) approved memantine administration for moderate to severe AD in 2003. This NMDA-receptor antagonist is the only one of its class for AD treatment, the remainder are cholinesterase inhibitors (Cummings et al., 2013). Glutamate binds to NMDA receptors on the cell, to allow calcium to flow into the cell, and facilitate cell signalling, learning and memory. However, an excess of glutamate from cell death results in the cell being overwhelmed with calcium, which is damaging. A non-competitive NMDA-receptor antagonist (memantine) mediates this excessive influx but maintains the typical process (Lipton, 2005).

MMN is modulated by the glutaminergic system, which relies on NMDA-receptor pathways (Korostenskaja, Nikulin, Kičić, Nikulina, & Kähkönen, 2007). Memantine, which acts as a NMDA-receptor antagonist, has been tested with healthy adults to assess the effect on MMN (Korostenskaja et al., 2007). The study found that memantine enhanced MMN amplitude, but had no effect on latency (Korostenskaja et al., 2007). Furthermore, the study suggested that the frontal cortex was differential affected by drug administration during MMN generation (Korostenskaja et al., 2007). These are interesting observations considering that, in the present study, MMN is reduced for adults with DS: 1. Compared to controls, 2. Who are older (40+); and 3. Who have shown greater cognitive decline. Therefore, based on the strong association between MMN and NMDA receptors (Korostenskaja et al., 2007), memantine administration would likely enhance MMN for adults with DS.

Memantine has been used previously in mouse-models of DS. In a Ts65Dn mouse model, acute memantine administration rescued cognitive deficits to do with fear conditioning (Costa, Scott-McKean, & Stasko, 2008). Prolonged administration (6 months) of memantine in Ts65Dn mice, provided functional but not physiological rescue of learning and memory processes (Lockrow, Boger, Bimonte-Nelson, & Granholm, 2011). The success of memantine administration in mouse models of DS has led researchers to test the drug with humans. Memantine was tested for 52 weeks in a randomised, double-blind, placebo-controlled clinical trial for adults with DS, over the age of 40 years (MEADOWS), but to no effect (Hanney et al., 2012). However, this clinical trial was primarily run to assess the restorative effects of memantine on DS-AD pathology. Furthermore the focus was on cognitive outcomes, which can: 1. Be confounded by ID, and 2. Take more than one year to recover (Boada et al., 2012; Costa, 2011). Therefore, it may be valuable to assess the effects of memantine on adults with DS, without a diagnosis of AD, in a preventative rather than reactive motion; then quantify the effects with an objective, physiological measure, such as MMN.

From a cognitive stand-point, the heavy frontal component to the memantine modulated MMN response (Korostenskaja et al., 2007) could be of interest considering the early frontal, functional compromise in DS-AD (Ball et al., 2008). MMN amplitude recovery could be used as an interim assessment before longer-term cognitive follow-ups, as sustained cognitive recovery is typically a protracted process (Boada et al., 2012; Costa, 2011). As a longer-term aim, the effects of memantine administration on MMN and cognitive recovery could be tracked at 5-year intervals, with a high-risk group (DS 40+ no AD), to see if AD development is modified. This is obviously a time-consuming and expensive undertaking, however there is a shortage of drug trial research to mediate DS-AD, despite this group being at huge risk (Hanney et al., 2012; Prasher, 2004).

7.7.5 Recommendations

Of the EEG measures explored in this thesis, MMN showed the most robust relationship with age and cognitive decline. Therefore, MMN should be the primary measure of interest in future investigations using this study design. The present thesis included a longitudinal component: a one-year cognitive follow-up. Due to the protracted nature of DS-AD, combined with the ID confound on performance, baseline measures are essential for investigations of cognitive decline with this group. Therefore future work should continue to employ longitudinal designs. In the context of the long time course and unclear timing of the onset of the pathology, repeated measures over longer time scales – starting years before the development of clinical symptoms, would be important.

An additional focus for future work might be the resting-state EEG data. The reasons for focusing on the resting-state data are threefold: 1. Considering ERP elicited with either auditory or visual stimuli, the acuity of these senses decline in older age, whereas resting-state data is stimulus-free; 2. As the attention-contingent ERP response (P3b) was so unsuccessful, focusing research efforts on task-free EEG paradigms seems prudent; 3. Successful biomarkers of AD are likely to be multi-modal (Humpel, 2011) and resting state EEG data most readily maps onto fMRI data, for example, in terms of exploring connectivity.

In conclusion, EEG is non-invasive, inexpensive, rapid to administer, and easy and safe to use repeatedly in the same individual, so future work would need not choose between resting state and MMN measures. Furthermore, biomarkers of AD are still at the fledgling stages of development so it would be prudent to be inclusive rather than exclusive at this stage. The key recommendation arising from this thesis would be to focus on employing passive (resting, MMN) EEG paradigms within longitudinal study designs.

7.8 Final conclusions

In conclusion, this thesis aimed to investigate the potential value of EEG measures for: 1. Evaluating the premature, neurological aging hypothesis of DS, and 2. Predicting cognitive decline. To achieve these aims, the thesis began by comparing EEG measures between adults with DS and TD controls: to evaluate the waveforms, and investigate premature aging. The thesis then focused on the DS group: to establish relationships between electrophysiology, executive dysfunction and cognitive decline. The findings from this thesis lay groundwork for future studies, which might elucidate disease mechanisms, and thus suggest drug targets, in premature aging and cognitive decline in DS.

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9 Appendices

Appendix A. Favourable ethical opinion letter

Health Research Authority
National Research Ethics Service
NRES Committee London – Queen Square
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

08 September 2014

Dear Ms Jennings

Study title: **Characterising aging effects on EEG indices of neurocognitive processes in adults with Down's Syndrome: identifying potential markers of Alzheimer's disease development**
REC reference: **14/LO/1411**
IRAS project ID: **150350**

Thank you for your letter of 4 September 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 04 September 2014

Documents received

The documents received were as follows:

- Participant Information Sheet for adults with Downs Syndrome v2
- Carer Information Sheet v3
- Control Participant Information Sheet v2

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Advertisement for controls]	1	04 May 2014
Covering letter on headed paper [Covering Letter]	1	16 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Provisional letter of insurance for the project]	1	18 June 2014
GP/consultant information sheets or letters [Letter to GP of control participants]	2	23 June 2014
GP/consultant information sheets or letters [Letter to GP of adults with DS]	2	23 June 2014
Letter from funder [Funding confirmation letter]	1	17 June 2013
Letters of invitation to participant [Invitation letter to adults with DS who have not previously participated in studies in the research group]	2	09 July 2014
Letters of invitation to participant [Invitation letter to adults with DS who have previously participated in studies in the research group]	2	09 July 2014
Other [Health Foundation Funding Letter]	1	25 June 2013

A Research Ethics Committee established by the Health Research Authority

Other [Marmaduke Sheild Award]		
Participant consent form [Consent form for adults with DS]	1	05 May 2014
Participant consent form [Consent form for controls]	1	04 May 2014
Participant consent form [Consultee for adults with DS declaration form]	1	04 May 2014
Participant information sheet (PIS) [Information sheet for consultees for adults with DS]	1	04 May 2014
Participant information sheet (PIS) [Photobooklet for adults with DS]	2	09 July 2014
Participant information sheet (PIS) [Carer Information Sheet]	3	04 September 2014
Participant information sheet (PIS) [Control participant Information Sheet]	2	04 October 2014
Participant information sheet (PIS) [PIS for adults with Downs Syndrome]	2	04 September 2014
REC Application Form [REC_Form_21072014]		21 July 2014
Research protocol or project proposal [Protocol]	5	25 June 2014
Summary CV for Chief Investigator (CI) [CV]	1	16 July 2014
Summary CV for supervisor (student research) [CV]	1	16 July 2014
Validated questionnaire [A systematic review on assessment instruments for dementia in persons with intellectual disabilities, including tests from the Cambridge Executive Functioning Assessment for People with Intellectual Disabilities; Oliver Memory Tests and CANTAB.]		
Validated questionnaire [Paper describing the validation of the SIB for adults with DS]	1	16 July 1998
Validated questionnaire		
Validated questionnaire [The Addenbrooke's Cognitive Examination Revised - to screen for dementia in the controls]		
Validated questionnaire [Paper describing the validation of the CAMDEX for adults with DS]	1	16 September 2004
Validated questionnaire [The Edinburgh Handedness Inventory]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/LO/1411	**Please quote this number on all correspondence**

Yours sincerely

R Heron

Rachel Heron
REC Manager

E-mail: nrescommittee.london-queensquare@nhs.net

Copy to: *Ms Sally Jennings*
Mr Stephen Kelleher, R&D Department

Appendix B. Invitation letter for the adults with DS

New Participant Invitation Letter version 2 – 09.07.14

CPFT UNIVERSITY OF CAMBRIDGE

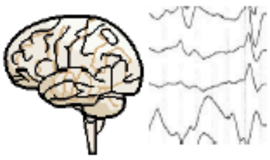
INVITATION LETTER

Brain Activity in Down's Syndrome

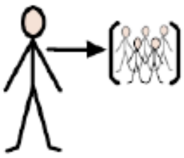
Dear

I am **Sally Jennings,** a PhD student at the University of Cambridge.

I am **researching**



How **brain activity** of people with Down's Syndrome changes with age.



I would like to ask you to take part in the **study.**

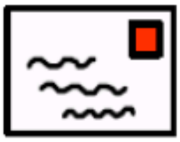
There is an **information sheet** for you to read, telling you about the study.

If you would like to **know more** or **take part** in the study

You can talk to **Sally Jennings**

01223 746 147

srj32@medschl.cam.ac.uk



or fill in a **reply slip** and post it to us.

Thank you,

Sally Jennings, PhD Student

Brain Activity in Down's Syndrome

Reply Slip

Please tick one of the boxes and put it in the envelope provided.

☐ I would like to find out more about the study.

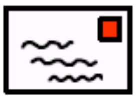
☐ I do not wish to take part.

Your contact details:

Your name

Name of the 'person that knows you best'

Please tick how you and 'the person that knows you best' would like to be contacted:



☐ Postal address:

☐ Telephone number:

☐ Email address:

Appendix C. Advertisement for typically developing control participants

Version 1/04.05.14

CPFT

UNIVERSITY OF CAMBRIDGE

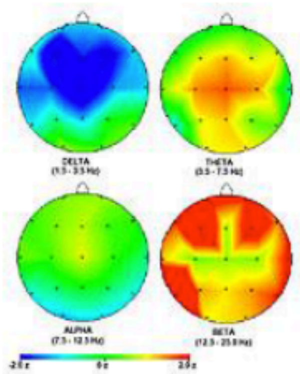
Brain Activity in Down's Syndrome

What is the study?

People with Down's Syndrome are at increased risk of developing Alzheimer's disease, and do so at younger ages, compared to the general population. This might be because amyloid is over-produced in Down's Syndrome and amyloid build-up plays a key role in the development of Alzheimer's disease. Electroencephalography (EEG) is a technology which records brain activity via electrodes applied to the scalp. The aim of this study is to investigate whether EEG has the potential to both measure the effects of aging on the brain and indicate early stages of Alzheimer's disease, in Down's Syndrome.

What will I be asked to do?

1. Agree to take part in the study as a healthy control.
2. Come to The Herchel Smith Building (Addenbrookes) in Cambridge.
3. Complete some short memory and cognitive measures
4. Wear an EEG cap whilst listening to some sounds.



How much time will it take?

The whole visit will take around three hours.

Will I be paid?

We will reimburse you **£20** for your time and reimburse your travel costs.

What do I do next?

If you would like to know more then **contact Sally** Jennings on:

01223 746 190

srj32@medschl.cam.ac.uk

Sally Jennings
01223746147
srj32@medschl.cam.ac.uk

Sally Jennings
01223746147
srj32@medschl.cam.ac.uk

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srj32@medschl.cam.ac.uk

Sally Jennings
01223746147
srj32@medschl.cam.ac.uk

Appendix D. Cross-sectional study information sheet for adults with DS

UNIVERSITY OF CAMBRIDGE

Cambridge Intellectual and Developmental Disabilities Research Group

PARTICIPANT INFORMATION SHEET

Brain Activity in Down's Syndrome

I am **Sally Jennings**, a PhD student at the University of Cambridge.

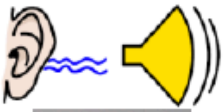
I am **researching**

How **brain activity** of people with Down's Syndrome changes with age.

We have asked you to take part because you have Down's Syndrome and are 20+ years old.

What will happen?

We would like you to do some **puzzles.**



We would like you to **listen** to some **sounds**.

You will be asked to wear a cap so we can record your brain activity.

You will be asked to **watch** a silent **movie**.

You **may** have a blood sample taken by a doctor or nurse.

Where?

On **day 1**, we will **visit you** and your parent or carer **at home**, or where is good for you.

On **day 2**, you and your parent or carer will **visit us** at the Herchel Smith Building, **Cambridge**.

Your rights

You do not have to **take part.** <u>You can say no.</u>

You can **stop** at anytime you want to.

Risk and benefits

The research may **help** other people like you.

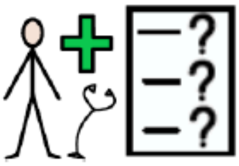
Taking part will **not harm** you.

Payment

You will be reimbursed **£20** for your time. We will also reimburse **travel costs** for you and your parent or carer, and an overnight stay if needed.

Confidentiality

Only the researcher will know your **name and address**.



If you tell us we can, we will **ask your doctor** whether you have: a genetic diagnosis of Down's Syndrome; a clinical diagnosis of dementia; hearing problems; epilepsy; psychiatric or neurological disorder(s); been given medication(s).

Results

Results will be written in **papers** and presented at **talks**. Only the researcher will know which results are yours.

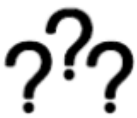
We may like to put some of your **answers** into papers and other studies but we won't use your name.

With your permission, we will **tell your doctor** if we find something wrong.

Ethical Approval

This project has been approved by the NHS Ethics Committee.

Questions



Do you have any questions?

Further Information

You can talk to **Sally Jennings**

01223 746 147

srj32@medschl.cam.ac.uk

Problems

If you have a problem you can also talk to

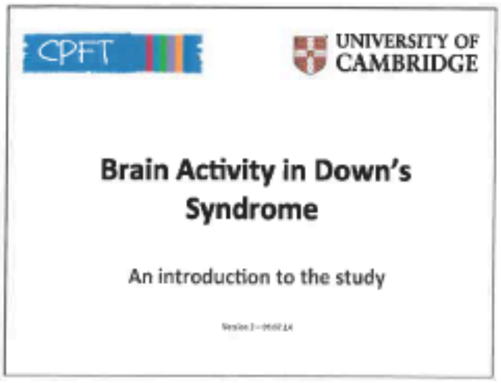
Dr Howard Ring

01223 746 121

Of if you feel we cannot help, you can talk to the **Patient Advice and Liaison Service.** They will help you with problems and to make a complaint.

0800 3760775

Appendix E: Cross-sectional study photo booklet for adults with DS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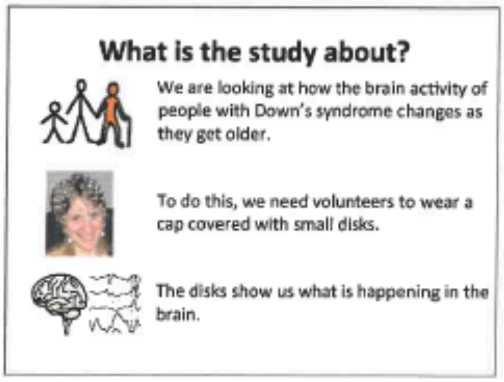
UNIVERSITY OF CAMBRIDGE

Brain Activity in Down's Syndrome

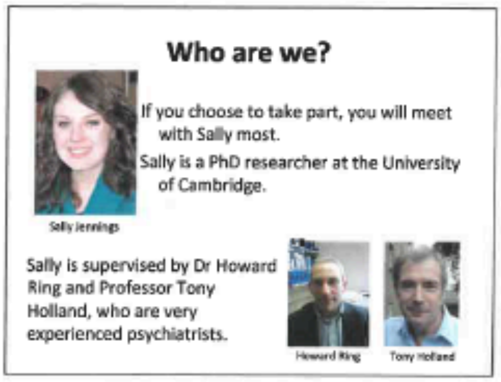
An introduction to the study


What is the study about?

We are looking at how the brain activity of people with Down's syndrome changes as they get older.

To do this, we need volunteers to wear a cap covered with small disks.

The disks show us what is happening in the brain.


Who are we?

If you choose to take part, you will meet with Sally most.

Sally is a PhD researcher at the University of Cambridge.

Sally Jennings

Sally is supervised by Dr Howard Ring and Professor Tony Holland, who are very experienced psychiatrists.

Howard Ring

Tony Holland


What will happen if I take part?

You will take part over **2 days**:

Day 1 we will **visit you** at your home, or where is good for you, with your parent or carer.

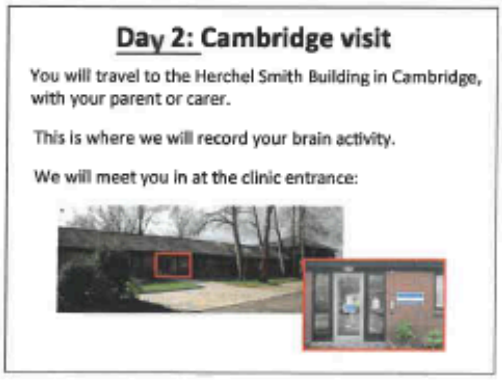
Day 2 you will **visit us** at Cambridge, with your parent or carer.


Day 1: home visit

We will visit you at your home, or somewhere else that is good for you, with your parent or carer.

We will ask some questions to find out more about you.

We will ask you to do some memory puzzles and games.


Day 2: Cambridge visit

You will travel to the Herchel Smith Building in Cambridge, with your parent or carer.

This is where we will record your brain activity.

We will meet you in at the clinic entrance:

Blood Sample

The Herchel Smith Building is part of Addenbrookes Hospital.

You may need to have a blood sample taken here, by a doctor or nurse.

The cap you will wear

Where you will sit

What you will do

Wear the cap

Listen to sounds

Watch a movie

Respond to the sounds

Where Sally will sit

Thanks!

If you have any more questions, **please contact Sally** on:

srj32@medschl.cam.ac.uk

01223 746147

Appendix F. Consultee information sheet preface (followed by appendix D)

Cambridge Intellectual and Developmental Disabilities Research Group

CONSULTEE INFORMATION SHEET

Brain Activity in Down's Syndrome

Dear ……………………

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research.

To help decide if he/she should join the study, we'd like to ask your opinion whether or not they would want to be involved. We'd ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the consultee declaration enclosed. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.

If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

We set out below the information sheet that will go to your relative/ friend.

Appendix G. Cross-sectional study information sheet for the carers of the participants with DS

Cambridge Intellectual and Developmental Disabilities Research Group

CARER INFORMATION SHEET

Brain Activity in Down's Syndrome

We would like to invite the person you support to take part in a research study. Please take time to read this sheet carefully for information.

Who are we?

We are a group of researchers and doctors from the Cambridge Intellectual and Developmental Disabilities Research Group at the University of Cambridge. This project is led by Sally Jennings who is undertaking it as part of her PhD training. It is supervised by Dr Howard Ring and Prof Tony Holland, both academic psychiatrists at the University of Cambridge.

What is this research about?

People with Down's Syndrome are at increased risk of developing Alzheimer's disease, and do so at younger ages, compared to the general population. Electroencephalography (EEG) is a technology which records brain activity through electrodes placed to the scalp. EEG is a promising candidate for screening 'at risk' populations because it is entirely safe, relatively cheap and undemanding for participants. The aim of this study is to investigate whether EEG has the potential to both measure the effects of aging on the brain and indicate early stages of Alzheimer's disease, in Down's Syndrome.

Why have we contacted you?

We have invited the individual you support to participate in this research because he/she has Down's Syndrome and is 20+ years old. If he/she decides to take part, your support will be vital since we request that a parent or carer is present at all visits. This is to make sure that participants are comfortable and well-looked after at all time. In our experience, this is best achieved by working alongside those who know a participant's individual needs best. We will also need to ask you some questions about the individual you care for, concerning their behaviour, as well as some things about their medical history.

What are the possible benefits of taking part?

There are no direct benefits to the person you support for taking part in this project. However, their participation in this research will help us to gain a better understanding of aging and the development of Alzheimer's disease in Down's syndrome.

What will happen if he/she decides to take part?

We will come to visit you and the person you support to talk about what they will be asked to do if they decide to take part. We will bring some photographs of equipment which we use to record their brain activity and other things they will see to help explain what it will be like to participate and ensure that he/she understands what will happen. Following this, if he/she decides to take part, we will ask him/her to sign a form saying that he/she understands what the study entails and would like to take part. This form is not binding and they are free to leave the study at any time.

The study takes place over two days. On the first day, we will come and visit you and the person you support at home, or another location which is convenient for you. We will begin by playing sounds and asking him/her to raise his/her hand upon hearing them. This screen for hearing loss will take about 5 minutes. We will then ask him/her to complete a handedness questionnaire, which will also take about 5 minutes. We will also ask you some questions about his/her daily functioning and medical history.

For people who have not recently participated in other studies conducted by the research group, we will ask him/her to complete some memory puzzles and games. This could take a maximum of 2 hours 40 minutes. However, there will be lots of breaks and they can finish the memory puzzles and games at the Cambridge visit.

On another day convenient for you both, we will ask you to accompany the person you support to the Herchel Smith Building, Cambridge. Here, people who have not previously participated in studies conducted by the research group will have a blood sample taken by a healthcare professional, which will take about 10 minutes. We will then record his/her brain activity by fitting a wetted EEG cap on his/her head. The EEG cap is entirely safe and not painful. However, as the cap will be wet we will place a towel around their shoulders to prevent any dampness to their shoulders. It will take about 30 minutes to ensure that the cap is fitted properly and to record the locations of all the electrodes on their head. We will then record 10 minutes of him/her at rest and 80 minutes of him/her listening to various sounds, through earphones, whilst watching a silent movie. Sometimes they will be asked to respond to the sounds using the response pad provided. We would ask you to sit with the researcher in the adjoining room. There will be lots of breaks which you can spend together.

Does he/she have to take part?

No, it is up to the person with Down's Syndrome whether you take part in this study. They can stop and leave the study at anytime. Leaving the study will not affect the care he/she receives.

Are there any risks of taking part?

There are no foreseeable safety issues as EEG is an entirely non-invasive procedure. Furthermore, you and the researcher will be able to see and hear the participant throughout testing via a webcam.

Will he/she be paid to take part?

We can pay for travel to and from Cambridge for both people with Down's Syndrome and their accompanying parent/carer. We will also pay for food and drink while in Cambridge. If an overnight stay is necessary because the distance to Cambridge is too great for a return journey to be feasible within the same day, we will cover the costs of this accommodation. We will also reimburse the person with Down's Syndrome £20 for their time.

What if you find that there is a problem?

We will ask him/her to sign a form consenting to us contacting his/her GP. Provided that he/she agrees, we will write to their GP to: 1. Let his/her GP know that he/she is taking part in this study. 2. Ask whether he/she has, and if so more details of: a genetic diagnosis of Down's Syndrome; a clinical diagnosis of dementia; clinically diagnosed hearing impairment(s); active, or history of, epilepsy; active, or history of, psychiatric or neurological disorder(s); currently being prescribed any medication(s). 3. Contact his/her GP in the unlikely event that we find something of medical relevance.

What if something goes wrong?

This study is approved by an NHS Research Ethics Committee and has insurance cover in case the person you support was harmed. This would mean that you can receive compensation if anything went wrong. It would not matter whether it was anyone's fault. This would be under the University's Clinical Trials policy.

If you, or the person you support, wish to complain about the way you, or they, have been treated in this study, you should be able to complain directly to the Chief Investigator of this study, Ms Sally Jennings (01223 746147), Dr Howard Ring (01223 746121) or Prof Tony Holland (01223 746121). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the National Health Service (01223 216756).

What will happen to the results of the research study?

All information about the person you support will be kept private. All the data collected in this study will be stored securely by the research team for up to 10 years. The results of the study will be published in scientific journals. No one will be able to tell that he/she took part in the study.

Who has reviewed the study?

This study was reviewed by the research team the University of Cambridge. It has also been reviewed by a group of people who awarded Sally Jennings a grant to carry out the study. We have the approval of the NHS Research Ethics Committee to do this study.

What to do if I, or the person I support, would like to know more?

Sally Jennings is the PhD researcher on the project. She is very happy to talk to you about the study and answer any questions you may have. You can contact Sally by:

Phone: 01223 746 147 or,

Email: srj32@medschl.cam.ac.uk .

Appendix H. Cross-sectional study information sheet for the control participants

Cambridge Intellectual and Developmental Disabilities Research Group

CONTROL PARTICIPANT INFORMATION SHEET

Brain Activity in Down's Syndrome

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read this sheet carefully. You should talk to others about the study if you wish.

Who are we?

We are a group of researchers and doctors from the Cambridge Intellectual and Developmental Disabilities Research Group at the University of Cambridge. This project is led by Sally Jennings who is undertaking it as part of her PhD training. It is supervised by Dr Howard Ring and Prof Tony Holland, both academic psychiatrists at the University of Cambridge.

What is this research about?

People with Down's Syndrome are at increased risk of developing Alzheimer's disease, and do so at younger ages, compared to the general population. Electroencephalography (EEG) is a technology which records brain activity through electrodes placed to the scalp. EEG is a promising candidate for screening 'at risk' populations because it is entirely safe, relatively cheap and undemanding for participants. The aim of this study is to investigate whether EEG has the potential to both measure the effects of aging on the brain and indicate early stages of Alzheimer's disease, in Down's Syndrome.

Why have I been chosen?

We have invited you to take part because you are healthy; do not have Down's syndrome and are over 20 years old.

What are the possible benefits of taking part?

There are no direct benefits to you by taking part in this project. Your participation in this research will help us to gain a better understanding of the development of Alzheimer's disease in Down's syndrome.

What will happen if I take part?

We will ask you to visit us at the Herchel Smith Building (part of Addenbrookes Hospital) at a time that suits you. We will ask you to sign a form saying that you understand what will happen and that you would like to take part. This form is not binding and you are free to leave the study at any time.

We will begin by playing sounds and asking you to raise your hand when you hear them. This screen for hearing loss will take about 5 minutes. We will then ask you to complete a handedness questionnaire, which will also take about 5 minutes. You will also complete two short tests of memory and problem solving, which will take around 35 minutes to carry out.

We will then record you brain activity by fitting a wetted EEG cap on your head. The EEG cap is entirely safe and not painful. However, as the cap will be wet we will place a towel around your shoulders to prevent any dampness to your shoulders. It will take about 30 minutes to ensure that the cap is fitted properly and to record the locations of all the electrodes on your head. We will then record 10 minutes of you at rest and 80 minutes of you listening to various sounds whilst watching a silent movie. Sometimes you will be asked to respond to the sounds using the response pad provided.

The whole study will take about 3 hours to complete.

Are there any risks of taking part?

There are no foreseeable safety issues as EEG is an entirely non-invasive procedure. Furthermore, the researcher will be able to see and hear you throughout testing via a web cam.

Do I have to take part?

No, it is up to you whether you take part in this study. If you would like to take part you will be asked to sign a consent form. You can stop and leave the study at anytime. Leaving the study will not affect the care you receive.

Will I be paid to take part?

We will pay for your travel expenses to and from the Herchel Smith Building for the research. We will also reimburse you £20 for your time.

What if you find that there is a problem?

We will ask you to sign a form consenting to us contacting your GP. Provided that you agree, we will write to your GP to: 1. Let your GP know that you are taking part in this study. 2. Ask whether you have, and if so more details of: clinically diagnosed hearing impairment(s); active, or history of, epilepsy; active, or history of, psychiatric or neurological disorder(s); currently being prescribed any medication(s). 3. Contact your GP in the unlikely event that we find something of medical relevance.

What if something goes wrong?

This study is approved by an NHS Research Ethics Committee and has insurance cover in case you were harmed. This would mean that you can receive compensation if anything went wrong. It would not matter whether it was anyone's fault. This would be under the University's Clinical Trials policy.

If you wish to complain about the way you have been treated in this study, you should be able to complain directly to the Chief Investigator of this study, Ms Sally Jennings (01223 746147), Dr Howard Ring (01223 746121) or Prof Tony Holland (01223 746121). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the National Health Service (01223 216756).

What will happen to the results of the research study?

All information about you will be kept private. All the data collected in this study will be stored securely by the research team for up to 10 years. The results of the study will be published in scientific journals. No one will be able to tell you took part in the study.

Who has reviewed the study?

This study was reviewed by the research team the University of Cambridge. It has also been reviewed by a group of people who awarded Sally Jennings a grant to carry out the study. We have the approval of an NHS Research Ethics Committee to do this study.

What to do if I would like to know more?

Sally Jennings is the PhD researcher on the project. She is very happy to talk to you about the study and answer any questions you may have. You can contact Sally by phone on 01223 746 147 or email on srj32@medschl.cam.ac.uk .

Appendix I. Longitudinal study information sheet for the participants with DS

UNIVERSITY OF CAMBRIDGE

Cambridge Intellectual and Developmental Disabilities Research Group

PARTICIPANT INFORMATION SHEET

Brain Activity in Down's Syndrome

Sally Jennings is a PhD student at the University of Cambridge.

You took part in a **research** study with Sally last year

about how the **brain activity** of people with Down's Syndrome changes with age.

What will happen?

Sally would like to **visit you** and your parent or carer **at home**, or where is good for you.

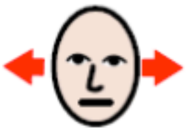
Where we would like to do some **puzzles.**

We are doing this **research** to see if

your brain activity **last year**

can **predict** how you answer the puzzles **this year**.

Your rights



You do not have to **take part.** You can say no.

You can **stop** at anytime you want to.

Risk and benefits

The research may **help** other people like you.

Taking part will **not harm** you.

Confidentiality

Only the researcher will know your **name and address**.

Results

Results will be written in **papers** and presented at **talks**. Only the researcher will know which results are yours.

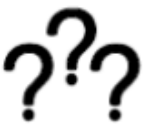
We may like to put some of your **answers** into papers but we won't use your name.

If you say we can, we will **tell your doctor** if we find anything wrong.

Ethical Approval

This project has been approved by the NHS Ethics Committee.

Questions

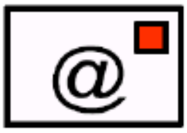


Do you have any questions?

Further Information

You can talk to **Sally Jennings**

01223 746 147



srj32@medschl.cam.ac.uk

Problems

If you have a problem you can also talk to

Dr Howard Ring

01223 746 121

Of if you feel we cannot help, you can talk to the **Patient Advice and Liaison Service.** They will help you with problems and to make a complaint.

0800 3760775

Appendix J. Longitudinal information sheet for the carers of the participating adults with DS

Cambridge Intellectual and Developmental Disabilities Research Group

CARER INFORMATION SHEET

Brain Activity in Down's Syndrome

We would like to invite the person you support to take part in a research study. Please take time to read this sheet carefully for information.

Who are we?

We are a group of researchers and doctors from the Cambridge Intellectual and Developmental Disabilities Research Group at the University of Cambridge. This project is led by Sally Jennings who is undertaking it as part of her PhD training. It is supervised by Dr Howard Ring and Prof Tony Holland, both academic psychiatrists at the University of Cambridge.

What is this research about?

People with Down's Syndrome are at increased risk of developing Alzheimer's disease, and do so at younger ages, compared to the general population. Electroencephalography (EEG) is a technology which records brain activity through electrodes placed to the scalp. EEG is a promising candidate for screening 'at risk' populations because it is entirely safe, relatively cheap and undemanding for participants. The aim of this study is to investigate whether EEG has the potential to both measure the effects of aging on the brain and indicate early stages of

Alzheimer's disease, in Down's Syndrome. The person you support participated in the EEG part of the study last year. This year we would like to do a follow-up cognitive assessment to explore to what extent EEG can predict future cognition.

Why have we contacted you?

We have invited the individual you support to participate in this research because he/she participated in the first part of the study last year. If he/she decides to take part, your support will be vital since we request that a parent or carer is present at all visits. This is to make sure that participants are comfortable and well-looked after at all times. In our experience, this is best achieved by working alongside those who know a participant's individual needs best. We will also need to ask you some questions about the individual you care for, concerning their behaviour, as well as some things about their medical history.

What are the possible benefits of taking part?

There are no direct benefits to the person you support for taking part in this project. However, their participation in this research will help us to gain a better understanding of aging and the development of Alzheimer's disease in Down's syndrome.

What will happen if he/she decides to take part?

We will come to visit you and the person you support to talk about what they will be asked to do if they decide to take part. We will explain what it will be like to participate and ensure that he/she understands what will happen. Following this, if he/she decides to take part, we will ask him/her to sign a form saying that he/she understands what the study entails and would like to take part. This form is not binding and they are free to leave the study at any time.

We will then ask him/her to complete some memory puzzles and games. This could take a maximum of 2 hours 40 minutes. However, there will be lots of breaks and they can finish the memory puzzles and games another day.

Does he/she have to take part?

No, it is up to the person with Down's Syndrome whether he/she takes part in this study. They can stop and leave the study at anytime. Leaving the study will not affect the care he/she receives.

Are there any risks of taking part?

There are no foreseeable safety issues as we will just be playing memory puzzles and games in a location of your choosing.

What if you find that there is a problem?

We will ask him/her to sign a form consenting to us contacting his/her GP. Provided that he/she agrees, we will write to their GP to: 1. Let his/her GP know that he/she is taking part in this study. 2. Contact his/her GP in the unlikely event that we find something of medical relevance.

What if something goes wrong?

This study is approved by an NHS Research Ethics Committee and has insurance cover in case the person you support was harmed. This would mean that you can receive compensation if anything went wrong. It would not matter whether it was anyone's fault. This would be under the University's Clinical Trials policy.

If you, or the person you support, wish to complain about the way you, or they, have been treated in this study, you should be able to complain directly to the Chief Investigator of this study, Ms Sally Jennings (01223 746147), Dr Howard Ring (01223 746121) or Prof Tony Holland (01223 746121). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the National Health Service (01223 216756).

What will happen to the results of the research study?

All information about the person you support will be kept private. All the data collected in this study will be stored securely by the research team for up to 10 years. The results of the study will be published in scientific journals. No one will be able to tell that he/she took part in the study.

Who has reviewed the study?

This study was reviewed by the research team the University of Cambridge. It has also been reviewed by a group of people who awarded Sally Jennings a grant to carry out the study. We have the approval of the NHS Research Ethics Committee to do this study.

What to do if I, or the person I support, would like to know more?

Sally Jennings is the PhD researcher on the project. She is very happy to talk to you about the study and answer any questions you may have. You can contact Sally by:

Phone: 01223 746 147 or,

Email: srj32@medschl.cam.ac.uk .

Appendix K. Information sheet for the carer's participation as CAMDEX informants

UNIVERSITY OF CAMBRIDGE

Cambridge Intellectual and Developmental Disabilities Research Group

CARER INFORMATION SHEET FOR PARTICIPATION

Brain Activity in Down's Syndrome

Who are we?

We are a group of researchers and doctors from the Cambridge Intellectual and Developmental Disabilities Research Group at the University of Cambridge. This project is led by Sally Jennings who is undertaking it as part of her PhD training. It is supervised by Dr Howard Ring and Prof Tony Holland, both academic psychiatrists at the University of Cambridge.

What is this research about?

People with Down's Syndrome are at increased risk of developing Alzheimer's disease, and do so at younger ages, compared to the general population. Electroencephalography (EEG) is a technology which records brain activity through electrodes placed to the scalp. EEG is a promising candidate for screening 'at risk' populations because it is entirely safe, relatively cheap and undemanding for participants. The aim of this study is to investigate whether EEG has the potential to both measure the effects of aging on the brain and indicate early stages of Alzheimer's disease, in Down's Syndrome. The person you support participated in the EEG part of the study last year. This year we would like to do a follow-up cognitive assessment to explore to what extent EEG can predict future cognition. As part of the follow-up cognitive assessment, we would also like to ask you some questions about his/her abilities.

Why have we contacted you?

The person you support is participating in the research study and, as the person that knows them best, we would like to ask you some questions about his/her abilities. Each question has two parts: first you will be asked if he/she has a problem in a particular area of function; then you will be asked whether this is a deterioration or whether he/she has always had a difficulty in this area. You will also be asked some questions about his/her medical history.

What are the possible benefits of taking part?

There are no direct benefits for taking part in this project. However, your participation in this research will help us to gain a better understanding of aging and the development of Alzheimer's disease in Down's syndrome.

What will happen if I to take part?

We will come to visit you to talk about what taking part involves. Following this, if you decide to participate, we will ask you to sign a form saying that you understand what the study entails and would like to take part. This form is not binding and you are free to leave the study at any time.

We will then ask you some questions about the abilities of the person you support. Each question has two parts: first you will be asked if he/she has a problem in a particular area of function; then you will be asked whether this is a deterioration or whether he/she has always had a difficulty in this area. You will also be asked some questions about his/her medical history. This will take between 30 minutes and 1 hour.

Do I have to take part?

No, you can stop and leave the study at anytime. You do not have to explain why.

Are there any risks of taking part?

There are no foreseeable safety issues as you will just be asked questions.

What if you find that there is a problem?

We will ask you to sign a form consenting for us to share your answers with the GP of the person you support, in the event that they are of medical relevance.

What if something goes wrong?

This study is approved by an NHS Research Ethics Committee and has insurance cover. This would mean that you can receive compensation if anything went wrong. It would not matter whether it was anyone’s fault. This would be under the University’s Clinical Trials policy.

If you wish to complain about the way have been treated in this study, you should be able to complain directly to the Chief Investigator of this study, Ms Sally Jennings (01223 746147), Dr Howard Ring (01223 746121) or Prof Tony Holland (01223 746121). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) at the National Health Service (01223 216756).

What will happen to the results of the research study?

All information will be kept private. Your relationship with the person you support, but not your name, will appear with your data. This is to provide context to your answers. All the data collected in this study will be stored securely by the research team for up to 10 years. The results of the study will be published in scientific journals. No one will be able to tell that you took part in the study.

Who has reviewed the study?

This study was reviewed by the research team the University of Cambridge. It has also been reviewed by a group of people who awarded Sally Jennings a grant to carry out the study. We have the approval of the NHS Research Ethics Committee to do this study.

What to do if I, or the person I support, would like to know more?

Sally Jennings is the PhD researcher on the project. She is very happy to talk to you about the study and answer any questions you may have. You can contact Sally by:

Phone: 01223 746 147 or,

Email: srj32@medschl.cam.ac.uk .

Appendix L. Cross-sectional study consent form for the participants with DS

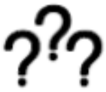
Participant Consent Form — version 2-28.10.14

Participant ID..............

PARTICIPANT CONSENT FORM

Brain Activity in Down's Syndrome Study

I agree that: 

		Yes	No
	I have **read** and **understand** the information sheet.	☐	☐
	I **understand** the **good** and **bad** things about taking part.	☐	☐
	I have had the chance to ask **questions.**	☐	☐
	I **understand** I **do not have** to **take part** and I can **stop** when I want.	☐	☐
	You can ask me to do some **puzzles.**	☐	☐
	You can record my **brain activity.**	☐	☐

		
	A doctor or nurse can take a **blood sample.**	Yes No
	You can **tell my doctor** that I am taking part in the study.	Yes No
	You can ask my doctor some questions about my **medical history.**	Yes No
	You can **tell my doctor** if you find something wrong.	Yes No
	I **agree** to **take part** in the study.	Yes No
	You can contact me about **other studies.**	Yes No
	You can use my results in **other studies**, which do **not have my name** on.	Yes No

Participant:

Name: ______________________________

Signature: ___________________________

Date: ______________________________

Person taking consent:

Name: ______________________________

Signature: ___________________________

Date: ______________________________

Participant ID: ....

CONSULTEE DECLARATION FORM

Brain Activity in Down's Syndrome

	YES	NO
1. I (name of consultee...) have been consulted about (name of potential participant...) participating in this research project. I have had the opportunity to ask **questions** about the study and **understand** what is involved.	☐	☐
2. In my opinion he/she would have **no objection** to taking part in the study.	☐	☐
3. I know that he/she **does not have to take part** and that **I can withdraw** them from the study **at any time** without telling the research team why.	☐	☐
4. I know that **all their data with be anonymised**. I understand that this will be stored in a locked place for up to ten years.	☐	☐
5. I understand that the **research team will have access** to their anonymised data.	☐	☐
6. I am happy for the research team to **write to their doctor** to **tell him/her** that he/she is **taking part** in this study.	☐	☐
7. I am happy for the research team to **write to their doctor** to ask **him/her** some questions about his/her **medical history**.	☐	☐
8. I am happy for the research team to **tell their doctor if the measures show that something might be wrong**.	☐	☐
9. I am happy for his/her **anonymised data to be used in other studies**.	☐	☐
10. I am happy for him/her to be **contacted** by the Down's Syndrome Research Group **about future studies**.	☐	☐
11. **I agree that** (name of potential participant...) **can take part in the study.**	☐	☐

Name of Consultee *(please print)*	Date	Time	Signature

Relationship to participant...

Name of researcher	Date	Time	Signature

Appendix N. Consent form for the control participants

CPFT

UNIVERSITY OF CAMBRIDGE

Participant ID: ....

CONTROL PARTICIPANT CONSENT FORM

Brain Activity in Down's Syndrome

	YES	NO
1. I have **read and understand the information sheet** dated .... (version ....) and have **had time to think** about whether I want to take part and **ask questions**.	☐	☐
2. I know that I **do not have to take part** if I don't want to and that I **can stop** taking part **at any time** without telling the research team why.	☐	☐
3. I know that **all my data with be anonymised**. I understand that this will be stored securely for up to ten years.	☐	☐
4. I understand that the **research team will have access** to my anonymised data.	☐	☐
5. I am happy for the research team to **write to my doctor** to **tell him/her** that I am **taking part** in this study.	☐	☐
6. I am happy for the research team to **write to my doctor** to **ask him/her** some questions about my **medical history**.	☐	☐
7. I am happy for the research team to **tell my doctor** if the measures show that something might be wrong.	☐	☐
8. I am happy for my **anonymised data to be used in other studies**.	☐	☐
9. I am happy to be **contacted** by the Down's Syndrome Research Group **about future studies**.	☐	☐
10. **I agree to take part in the study.**	☐	☐

Name of participant *(please print)*	Date	Time	Signature
Name of researcher	Date	Time	Signature

Appendix O. Longitudinal study consent form for the participants with DS

Participant Consent Form – cognitive follow up
version 1-19.11.15

CPFT

UNIVERSITY OF CAMBRIDGE

PARTICIPANT CONSENT FORM

Brain Activity in Down's Syndrome Study

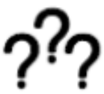
<u>**I agree that:**</u>

I have **read** and **understand** the information sheet.

Yes No
☐ ☐

I **understand** the **good** and **bad** things about taking part.

Yes No
☐ ☐



I have had the chance to ask **questions**.

Yes No
☐ ☐

I **understand** I **do not have** to **take part** and I can **stop** when I want.

Yes No
☐ ☐

You can ask me to do some **puzzles**.

Yes No
☐ ☐

You can use my results in **other studies**, which do **not have my name** on.

Yes No
☐ ☐

You can **tell my doctor** that I am taking part in the study, and if you find something wrong. Yes ☐ No ☐

I **agree** to **take part** in the study. Yes ☐ No ☐

You can **contact** me about **future studies** Yes ☐ No ☐

Participant:

Name: ______________________________

Signature: ______________________________

Date: ______________________________

Person taking consent:

Name: ______________________________

Signature: ______________________________

Date: ______________________________

Appendix P. Consent form for the carer's participation as CAMDEX informants

CPFT

UNIVERSITY OF CAMBRIDGE

CARER CONSENT FORM

Brain Activity in Down's Syndrome

	YES	NO
1. I have **read and understand the information sheet** dated .... (version ....) and have **had time to think** about whether I want to take part and **ask questions**.	☐	☐
2. I know that I **do not have to take part** if I don't want to and that I **can stop** taking part **at any time** without telling the research team why.	☐	☐
3. I am happy that my relationship with the participant, but **not my name**, will appear with my data.	☐	☐
4. I understand that my data will be **stored securely** for up to ten years.	☐	☐
5. I understand that the **research team will have access** to my data.	☐	☐
6. I am happy for my **data** to be **used in other studies**.	☐	☐
7. I am happy for you to **share my data with the doctor** of the person I support.	☐	☐
8. I am happy to be **contacted** by the Down's Syndrome Research Group **about future studies**.	☐	☐
9. **I agree to take part in the study.**	☐	☐

Name of participant *(please print)*	Date	Time	Signature

Name of researcher	Date	Time	Signature

Appendix Q: age- and gender- matching

DS		TD	
Age range	**N**	**Age range**	**N**
20-30	11	20-30	10
30-40	10	30-40	7
40-50	11	40-50	14
50-60	5	50-60	9
Sex	**N**	**Sex**	**N**
M	20	M	17
F	16	F	22

DS Age (years)	DS Sex	TD age (years)	TD Sex
22	M	20	M
22	F	23	F
22	M	24	M
24	M	25	M
25	F	25	M
25	F	26	M
26	M	27	F
27	F	27	F
28	M	27	M
29	M	29	F
29	M	30	F
30	F	31	F
33	F	32	M
34	M	33	F
35	M	34	M
35	M	37	F
35	F	38	M
35	F	40	F
36	F	43	M
37	M	44	M
38	M	44	F
40	M	44	M
42	F	44	M
43	M	45	M
43	F	46	F
43	M	46	F
44	M	47	F
45	F	47	M
45	F	48	M
45	M	49	F
46	M	50	F
46	M	50	F
50	M	51	F
51	F	53	F
51	F	54	F
55	F	56	M
		57	F
		58	F
		59	F

Appendix R. ACE-R

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing: .... /....... /.......
Tester's name: ....
Age at leaving full-time education: ....
Occupation: ....
Handedness: ....

ORIENTATION

➢ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
	....	....	....	....	....	
➢ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]
	....	....	....	....	....	

REGISTRATION

[Score 0-3]

➢ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials ....

ATTENTION & CONCENTRATION

[Score 0-5] (for the best performed task)

➢ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

➢ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

ATTENTION & ORIENTATION

MEMORY - Recall

[Score 0-3]

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

MEMORY - Anterograde Memory

[Score 0-7]

➢ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	....	....	....
Devon	....	....	....

MEMORY - Retrograde Memory

[Score 0 -4]

➢ Name of current Prime Minister ....
➢ Name of the woman who was Prime Minister ....
➢ Name of the USA president ....
➢ Name of the USA president who was assassinated in the 1960's ....

MEMORY

VERBAL FLUENCY - Letter 'P' and animals

➤ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7]

>17	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
<2	0
total	correct

➤ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7]

>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

FLUENCY

LANGUAGE - Comprehension

➤ Show written instruction:

[Score 0-1]

Close your eyes

➤ 3 stage command:

'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3]

LANGUAGE - Writing

➤ Ask the subject to make up a sentence and write it in the space below:

Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1]

LANGUAGE

L A N G U A G E - Repetition

➢ Ask the subject to repeat: **' hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less.

[Score 0-2]

➢ Ask the subject to repeat: **'Above, beyond and below'**

[Score 0-1]

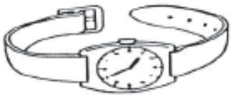
➢ Ask the subject to repeat: **'No ifs, ands or buts'**

[Score 0-1]

L A N G U A G E - Naming

➢ Ask the subject to name the following pictures:

[Score 0-2]
pencil +
watch

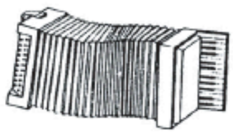




[Score 0-10]









L A N G U A G E

L A N G U A G E - Comprehension

➢ Using the pictures above, ask the subject to:

- Point to the one which is associated with the monarchy __________
- Point to the one which is a marsupial __________
- Point to the one which is found in the Antarctic __________
- Point to the one which has a nautical connection __________

[Score 0-4]

LANGUAGE - Reading

- Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1]

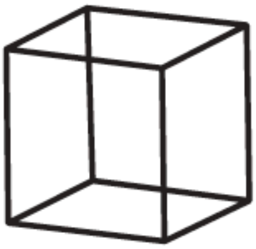
sew
pint
soot
dough
height

L A N G U A G E

VISUOSPATIAL ABILITIES

- Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1]

- Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2]



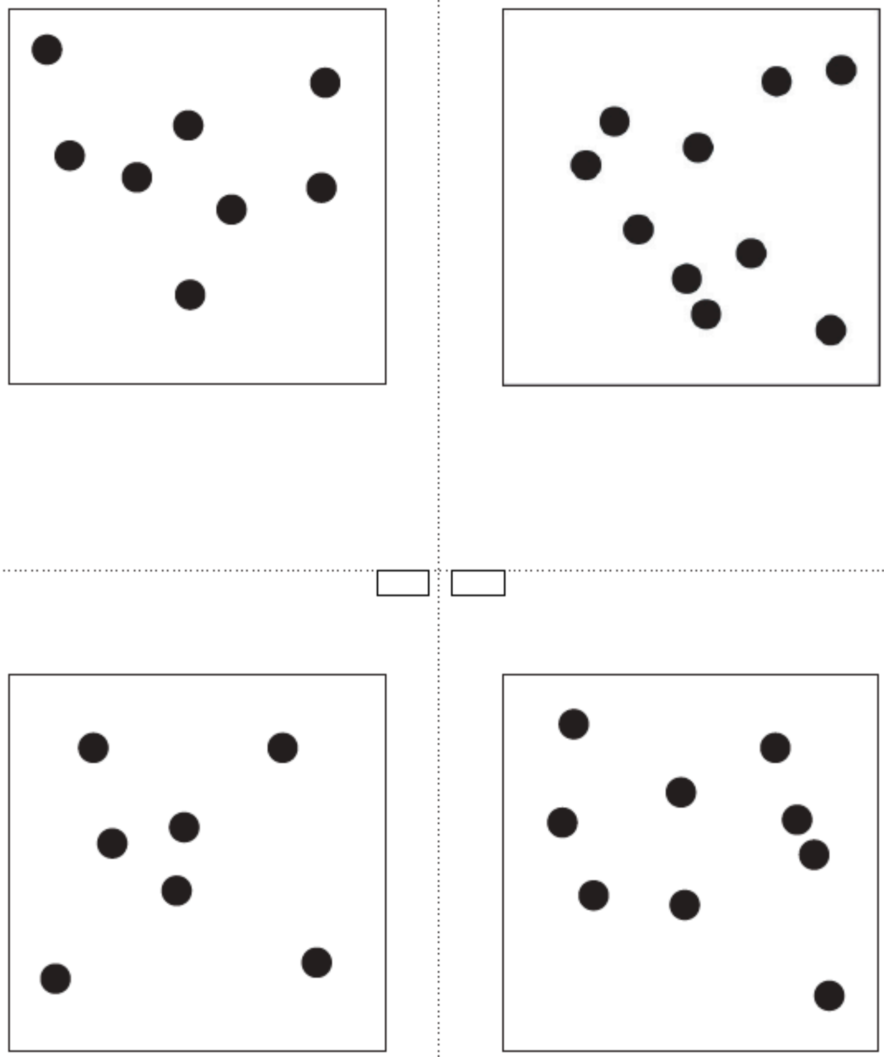
- Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5]

V I S U O S P A T I A L

PERCEPTUAL ABILITIES

➢ Ask the subject to count the dots without pointing them

[Score 0-4]



VISUOSPATIAL

Appendix S. CAMDEX-DS: Informant interview

BACKGROUND INFORMATION

Patient / Participant Details

1	**Name**		
2	**Address**		
3	**Referral source**	Self	1
		Relative	2
		Carer	3
		GP	4
		Inpatient Service	5
		Consultant / Specialist	6
		Other (specify)	7
4	**Reason for Assessment**	Clinical	1
		Research	2
5	**Date of Birth**		
6	**Age at Assessment**		
7	**Sex**	Male	1
		Female	2
8	**Current marital status**	Single	1
		Married	2
		Widowed	3
		Divorced	4
		Cohabiting	5
9	**Living arrangements**	Long-term hospital	1
		Nursing home	2
		Residential home	3
		Sheltered accommodation	4
		Supported Living	5
		Home with relative	6
		Own home with partner	7
		Own home alone	8
		Other	9

SECTION 1 INFORMANT INTERVIEW

This interview should be conducted with a relative, friend or carer who has known the patient / participant for at least 6 months, in order that they are able to comment on changes in functional ability or behaviour over time.

Each question should be asked as written. Additional questions may sometimes be necessary to clarify inadequate answers.

All items must be coded	***Code:***	
	Informant doesn't know **(DK)**	*8 or 88*
	Not asked/not applicable **(N/A)**	*9 or 99*

Informant Details

10	**Date of interview**	[ ][ ][ ]	
11	**Informant's name**	[ ]	
12	**Informant's address**	[ ]	
13	**How was the interview conducted?**	Face to face	**1**
		Telephone	**2**
14	**What is your relationship to _______ ?**	Parent	**1**
		Sibling	**2**
		Spouse	**3**
		Other relative	**4**
		Friend	**5**
		Carer/keyworker	**6**
		Other (specify)	**7**
15	**How long have you known him/her?**	|__|__| Years |__|__|	Months
16	**How often do you see him/her?**	Lives with	**1**
		Daily	**2**
		More than once a week	**3**
		At least once a week	**4**
		At least once a month	**5**
		At least once a year	**6**

Part 1 Patient/participant's Best Level of Functioning

Instructions to be read to informant:

"The aim of the next set of questions I am going to ask, is to find out about ....'s abilities when he/she was functioning **at his/her best** (before any decline in function). If there has been no decline, this will be as he/she is functioning now."

A EDUCATION AND EMPLOYMENT

17	Has he/she ever attended school?	No 0 DK 8 N/A 9	Yes, special school Yes, special class in mainstream Yes, mainstream	1 2 3	
18	If 'yes', for how long did she attend?	DK 88 N/A 99	|__|__| Years	|__|__|	Months
19	Has he/she ever attended college or day centre?	No 0 DK 8 N/A 9	Yes 1		
20	If 'yes', for how long did she attend?	DK 88 N/A 99	|__|__| Years	|__|__|	Months
21	Has he/she ever had a job?	No 0 DK 8 N/A 9	Yes 1	*If 'yes', give details:*	

B BASIC SKILLS

22	Has he/she ever been able to speak?	No 0 DK 8 N/A 9	Yes, single words only Yes, limited speech Yes, good speech	1 2 3
23	Has he/she ever been able to understand spoken language?	No 0 DK 8 N/A 9	Yes, single words only Yes, limited understanding Yes, good understanding	1 2 3
24	Has he/she ever been able to read?	No 0 DK 8 N/A 9	Yes, a little, familiar words Yes, good reader	1 2

25	Has he/she ever been able to write?	No DK N/A	0 8 9	Yes, name only or copies Yes, a little Yes, writes well	1 2 3
26	Has he/she ever been able to add up?	No DK N/A	0 8 9	Yes, a little Yes, good at sums	1 2

C INDEPENDENT LIVING

27	Has he/she ever been able to choose what to wear and dress him/herself?	No DK N/A	0 8 9	Yes, with support Yes, independently	1 2
28	Has he/she ever been able to prepare hot drinks or basic meals?	No DK N/A	0 8 9	Yes, with support Yes, independently	1 2
29	Has he/she ever been able to travel on public transport?	No DK N/A	0 8 9	Yes, with support Yes, independently	1 2
30	Has he/she ever been able to do housework e.g. dusting, dishwashing etc.?	No DK N/A	0 8 9	Yes, with support Yes, independently	1 2
31	Has he/she ever been able to go shopping?	No DK N/A	0 8 9	Yes, accompanied Yes, independently for small purchases only Yes, independently	1 2 3
32	Has he/she ever been able to use the telephone?	No DK N/A	0 8 9	Yes, answers only Yes, dials well known numbers Yes, independently	1 2 3

Part 2 Cognitive and Functional Decline

Instructions to be read to informant:

"The aim of the next set of questions, is to find out about changes in ....'s abilities, personality and behaviour.

These changes do not always appear in later life and may not be relevant to him/her, but we ask everyone the same questions because the replies might prove valuable in helping people who do have difficulties.

Each question has two parts. First I will ask you whether he/she has a problem in a particular area of function; then I will ask you whether this is a deterioration or whether he/she has always had difficulty in this area."

Questions are divided into subsections according to different areas of function, that are directly linked to diagnostic criteria for dementia on page 53 of this pack.

For each question, if no difficulty is established in part a) code part b) as 9 and move on to the next question.

Where deterioration is present, please record any examples given.

A EVERYDAY SKILLS

33	a) Does he/she have difficulties with his/her usual daytime activities at work, college or day centre? *Examples of change:*	Yes 1 ➔ No 0 DK 8 N/A 9	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
34	a) Does he/she have difficulty with a special skill or hobby? *Examples of change:*	Yes 1 ➔ No 0 DK 8 N/A 9	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
35	a) Does he/she have difficulty with shopping? *Examples of change:*	Yes 1 ➔ No 0 DK 8 N/A 9	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2

36	a) Does he/she have difficulty making a cup of tea? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
37	a) Does he/she have difficulty with housework e.g. dusting, dishwashing? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
38	a) Does he/she have difficulty preparing simple meals / snacks? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
39	a) Does he/she have difficulty using the telephone? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2

If there is no deterioration in everyday skills skip to section B and code questions 40 and 41 as 9

40	How long ago did you first notice this deterioration in everyday skills? *Record number of months and code as applicable*	I___I___I months	< 6 Months 0 DK 8 N/A 9	> 6 Months 1
41	Did the deterioration happen gradually or did it come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual 1

B MEMORY AND ORIENTATION

Memory

42	a)	Does he/she have difficulty remembering recent events e.g. when he/she last saw you or what happened the day before? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2			
43	a)	Does he/she often have difficulty remembering where he/she has left things? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2			
44	a)	Does he/she have difficulty remembering what has been said and repeat the same question over and over? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2			
45	a)	Does he/she have difficulty in remembering short lists of items, e.g. shopping? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2			
46	a)	Does he/she have difficulty remembering significant events from his/her past? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2			

47	a) Does he/she have difficulty remembering the names of close friends, relatives or carers? *Examples of change:*	Yes No DK N/A	1 0 8 9	→	b) Is this a deterioration?	Yes No DK N/A	1 0 8 9	→	Slight deterioration Great deterioration	1 2

Orientation

48	a) Does he/she have difficulty in interpreting surroundings, e.g. knowing where he/she is? *Examples of change:*	Yes No DK N/A	1 0 8 9	→	b) Is this a deterioration?	Yes No DK N/A	 0 8 9	→	Slight deterioration Great deterioration	1 2
49	a) Does he/she have difficulty finding the way around the neighbourhood, e.g. to the shops or Post Office near home? *Examples of change:*	Yes No DK N/A	1 0 8 9	→	b) Is this a deterioration?	Yes No DK N/A	 0 8 9	→	Slight deterioration Great deterioration	1 2
50	a) Does he/she have difficulty finding the way around the home (or ward), e.g. finding the toilet? *Examples of change:*	Yes No DK N/A	1 0 8 9	→	b) Is this a deterioration?	Yes No DK N/A	 0 8 9	→	Slight deterioration Great deterioration	1 2
51	a) Does he/she have difficulty knowing what day it is? *Examples of change:*	Yes No DK N/A	1 0 8 9	→	b) Is this a deterioration?	Yes No DK N/A	 0 8 9	→	Slight deterioration Great deterioration	1 2

52	a) Does he/she have difficulty knowing what time of day it is?	Yes 1 →	b) Is this a deterioration?	Yes →	Slight deterioration 1
		No 0		No 0	Great deterioration 2
		DK 8		DK 8	
		N/A 9		N/A 9	
	Examples of change:				

If there are no changes in memory and orientation skip to section C and code questions 53 - 56 as 9

53	How long ago did you first notice this deterioration in memory and orientation skills? *Record number of months and code as applicable*	|__|__| months	< 6 Months 0 DK 8 N/A 9	> 6 Months 1
54	Did the deterioration happen gradually or did it come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual 1
55	Do these changes interfere with his/her everyday activities?		No 0 DK 8 N/A 9	Yes 1
56	Do you think that he/she is aware of this memory problem?		No 0 DK 8 N/A 9	Yes 1

C1 OTHER COGNITIVE SKILLS

General Mental Functioning

57	a) Does he/she find it difficult to keep his/her mind on things? Is he/she easily distracted?	Yes 1 →	b) Is this a deterioration?	Yes →	Slight deterioration 1
		No 0		No 0	Great deterioration 2
		DK 8		DK 8	
		N/A 9		N/A 9	
	Examples of change:				

58	a) Does his/her thinking seem slow? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes No 0 DK 8 N/A 9	➔	Slight deterioration 1 Great deterioration 2
59	a) Does his/her thinking seem muddled? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes No 0 DK 8 N/A 9	➔	Slight deterioration 1 Great deterioration 2

Language

60	a) Does he/she have difficulty with reading? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes No 0 DK 8 N/A 9	➔	Slight deterioration 1 Great deterioration 2
61	a) Does he/she have difficulty in following instructions? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes No 0 DK 8 N/A 9	➔	Slight deterioration 1 Great deterioration 2
62	a) Does he/she have difficulty in keeping up with ordinary conversation? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes No 0 DK 8 N/A 9	➔	Slight deterioration 1 Great deterioration 2

63	a) Does he/she have difficulty with writing?	Yes 1	➔	b) Is this a deterioration?	Yes	➔	Slight deterioration 1 Great deterioration 2
		No 0 DK 8 N/A 9			No 0 DK 8 N/A 9		
	Examples of change:						
64	a) Does he/she speak very little?	Yes 1	➔	b) Is this a deterioration?	Yes	➔	Slight deterioration 1 Great deterioration 2
		No 0 DK 8 N/A 9			No 0 DK 8 N/A 9		
	Examples of change:						
65	a) When speaking, does he/she have difficulty in finding the right word or use wrong words?	Yes 1	➔	b) Is this a deterioration?	Yes	➔	Slight deterioration 1 Great deterioration 2
		No 0 DK 8 N/A 9			No 0 DK 8 N/A 9		
	Examples of change:						

Perception

66	a) Does he/she have difficulty identifying or recognising objects?	Yes 1	➔	b) Is this a deterioration?	Yes	➔	Slight deterioration 1 Great deterioration 2
		No 0 DK 8 N/A 9			No 0 DK 8 N/A 9		
	Examples of change:						
67	a) Does he/she have difficulty identifying or recognising people?	Yes 1	➔	b) Is this a deterioration?	Yes	➔	Slight deterioration 1 Great deterioration 2
		No 0 DK 8 N/A 9			No 0 DK 8 N/A 9		
	Examples of change:						

Praxis

68	a) Does he/she have difficulty carrying out familiar complex tasks (such as getting dressed) despite the physical ability to do them? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9		Slight deterioration 1 Great deterioration 2	

Executive Functions

69	a) Does he/she have difficulty in planning ahead and thinking about the future? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2	
70	a) Does he/she find it difficult to make decisions? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2	
71	a) Does he or she have difficulty solving day-to-day problems? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2	

If there are no changes in other cognitive skills skip to section C2 and code questions 72 and 73 as 9

72	How long ago did you first notice this deterioration in abilities? *Record number of months and code as applicable.*	|___|___| months	< 6 Months 0 DK 8 N/A 9	> 6 Months	1
73	Did the deterioration happen gradually or did it come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual	1

C2 PERSONALITY, BEHAVIOUR AND SELF CARE

Personality and Behaviour

74	a) Does he/she behave in a manner that leads to social difficulties? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration Great deterioration	1 2
75	a) Would you describe him/her as lacking in personality? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration Great deterioration	1 2
76	a) Does he/she show little emotion? Would you describe him/her as emotionally flat? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	➔	b) Is this a deterioration?	Yes ➔ No 0 DK 8 N/A 9	Slight deterioration Great deterioration	1 2

77	a)	Is he/she changeable in mood? i.e. Does he/she have rapid shifts between different emotions? *Examples of change:*	Yes No DK N/A	1 0 8 9	➔	b)	Is this a deterioration?	Yes No DK N/A	➔ 0 8 9	Slight deterioration Great deterioration	1 2
78	a)	Does he/she show a lack of enthusiasm for his/her usual interests? *Examples of change:*	Yes No DK N/A	1 0 8 9	➔	b)	Is this a deterioration?	Yes No DK N/A	➔ 0 8 9	Slight deterioration Great deterioration	1 2
79	a)	Is he/she often irritable or angry? *Examples of change:*	Yes No DK N/A	1 0 8 9	➔	b)	Is this a deterioration?	Yes No DK N/A	➔ 0 8 9	Slight deterioration Great deterioration	1 2
80	a)	Does he/she show a lack of concern for other people? *Examples of change:*	Yes No DK N/A	1 0 8 9	➔	b)	Is this a deterioration?	Yes No DK N/A	➔ 0 8 9	Slight deterioration Great deterioration	1 2
81	a)	Does he/she act impulsively, by doing the first thing that comes to mind? *Examples of change:*	Yes No DK N/A	1 0 8 9	➔	b)	Is this a deterioration?	Yes No DK N/A	➔ 0 8 9	Slight deterioration Great deterioration	1 2

82	**a)** Is he/she stubborn or perhaps a little awkward?	Yes **1** No **0** DK **8** N/A **9**	➔	**b)** Is this a deterioration?	Yes ➔ No **0** DK **8** N/A **9**	Slight deterioration Great deterioration	**1** **2**
	Examples of change:						
83	**a)** Does he/she get involved in difficult or embarrassing situations in public because of his/her behaviour?	Yes **1** No **0** DK **8** N/A **9**	➔	**b)** Is this a deterioration?	Yes ➔ No **0** DK **8** N/A **9**	Slight deterioration Great deterioration	**1** **2**
	Examples of change:						
84	**a)** Does he/she engage in inappropriate sexual behaviour?	Yes **1** No **0** DK **8** N/A **9**	➔	**b)** Is this a deterioration?	Yes ➔ No **0** DK **8** N/A **9**	Slight deterioration Great deterioration	**1** **2**
	Examples of change:						
85	**a)** Is he/she very restless? For example does he/she find it hard to sit down for any length of time?	Yes **1** No **0** DK **8** N/A **9**	➔	**b)** Is this a deterioration?	Yes ➔ No **0** DK **8** N/A **9**	Slight deterioration Great deterioration	**1** **2**
	Examples of change:						
86	**a)** Does he/she repeat the same word or phrase over and over again?	Yes **1** No **0** DK **8** N/A **9**	➔	**b)** Is this a deterioration?	Yes ➔ No **0** DK **8** N/A **9**	Slight deterioration Great deterioration	**1** **2**
	Examples of change:						

87		Does he/she develop routines from which he/she cannot easily be discouraged? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
88	a)	Does he/she often try to eat far too much? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2
89	a)	Does he/she try to eat peculiar things, such as soap, cigarettes or dirt? *Examples of change:*	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2

If there are no changes in personality skip to question 93 and code questions 90 – 92 as 9

90	How long ago did you first notice these changes in personality and/or behaviour? *Record number of months and code as applicable.*	I___I___I months	< 6 Months 0 DK 8 N/A 9	> 6 Months 1
91	Have these changes developed gradually or did they come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual 1
92	Do you think that he/she is aware of these problems?		No 0 DK 8 N/A 9	Yes 1

Self Care

93	a) Does he/she have difficulty feeding him/herself?							
	Yes, has to be fed	1	→	b) Is this a deterioration?	Yes	→	Slight deterioration	1
	Yes, eats simple solids e.g. biscuits	2					Great deterioration	2
	Yes, eats messily with spoon only	3						
	No	0			No	0		
	DK	8			DK	8		
	N/A	9			N/A	9		
94	a) Does he/she have difficulty in dressing or undressing?							
	Yes, needs major assistance	1	→	b) Is this a deterioration?	Yes	→	Slight deterioration	1
	Yes, needs moderate assistance	2					Great deterioration	2
	Yes, needs minor assistance	3						
	No	0			No	0		
	DK	8			DK	8		
	N/A	9			N/A	9		
95	a) Does he/she have difficulty with grooming, e.g. combing hair, shaving?							
	Yes, needs major assistance	1	→	b) Is this a deterioration?	Yes	→	Slight deterioration	1
	Yes, needs moderate assistance	2					Great deterioration	2
	Yes, needs minor assistance	3						
	No	0			No	0		
	DK	8			DK	8		
	N/A	9			N/A	9		
96	a) Does he/she have difficulty with bathing or showering?							
	Yes, needs major assistance	1	→	b) Is this a deterioration?	Yes	→	Slight deterioration	1
	Yes, needs moderate assistance	2					Great deterioration	2
	Yes, needs minor assistance	3						
	No	0			No	0		
	DK	8			DK	8		
	N/A	9			N/A	9		

97	a) Does he/she wet or soil him/herself? Yes, is doubly incontinent 1 Yes, wets often 2 Yes, wets occasionally 3 No 0 DK 8 N/A 9	→ b) Is this a deterioration?	Yes → No 0 DK 8 N/A 9	Slight deterioration 1 Great deterioration 2

If there are no changes in self care skills skip to section D and code questions 98 and 99 as 9

98	How long ago did you first notice this deterioration in self care skills? *Record number of months and code as applicable.*	|___|___| months	< 6 Months 0 DK 8 N/A 9	> 6 Months 1
99	Has this deterioration happened gradually or did it come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual 1

D GENERAL SUMMARY

If no cognitive or functional decline has been established, skip to part 3 and code 100 - 102 as 9

100	Since the onset of the difficulties we have talked about, has he/she had difficulty with mobility?	No 0 DK 8 N/A 9	Yes 1
101	Can you tell me what was the first change you noticed? *Record answer in full*	DK 8 N/A 9	Memory 1 Other cognitive 2 Personality 3 Everyday Skills 4 Other 5
102	How long ago did this first occur?	DK 8 N/A 9	|___|___| months

Part 3 Current Mental Health

Instructions to be read to informant:

"The aim of the next set of questions, is to find out about ....'s mental health."

A DEPRESSION

103	a)	Does he/she show a lack of interest or enjoyment in things in general?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
104	a)	Does he/she prefer to remain on his/her own rather than seek the company of others?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
105	a)	Is he/she lacking in energy? Does he/she find it hard to get things done?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
106	a)	Does he/she have difficulty in getting to sleep?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
107	a)	Does he/she wake early in the morning and fail to get to sleep again?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
108	a)	Does he/she sleep a lot by day?	Yes 1 No 0 DK 8 N/A 9	→	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1

109	a) Does he/she often cry?	Yes 1 →	b) Is this a change?	No 0 DK 8 N/A 9	Yes 1
		No 0 DK 8 N/A 9			
110	Does he/she talk more slowly than is usual for him/her?			No 0 DK 8 N/A 9	Yes 1
111	Has he/she lost his/her appetite or become much more hungry than usual?			No 0 DK 8 N/A 9	Yes 1
112	Do you think he/she is depressed?			No 0 DK 8 N/A 9	Yes 1

If no depression, skip to section B and code 113 – 118 as 9

113	How long has this depression been present?	I___I___I months	< 6 months 0 DK 8 N/A 9	> 6 months 1
114	Is there any reason why he/she has become depressed? *Specify:*		No 0 DK 8 N/A 9	Yes, bereavement 1 Yes, other 2
115	Is the depression so bad that it affects every part of his/her life, friendship or family life?		No 0 DK 8 N/A 9	Yes 1
116	When he/she is feeling depressed, can anything cheer him/her up?		No 0 DK 8 N/A 9	Yes 1
117	Is depression worse in the morning?		No 0 DK 8 N/A 9	Yes 1
118	Does he/she feel other people are to blame for his/ her unhappiness?		No 0 DK 8 N/A 9	Yes 1

B ANXIETY

119	a) Does he/she tend to worry a lot about little things?	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a change?	No 0 DK 8 N/A 9	Yes	1
120	a) Have there been times lately when he/she was very anxious or frightened? *Describe:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a change?	No 0 DK 8 N/A 9	Yes	1
121	a) Are there particular situations that make him/her anxious, e.g. going into shops or crowds? *Describe:*	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a change?	No 0 DK 8 N/A 9	Yes	1
122	a) Has he/she suffered from panic attacks, when he/she felt he/she would collapse or lose control of him/herself?	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a change?	No 0 DK 8 N/A 9	Yes	1

If no anxiety, skip to section D3 and code 124 and 125 as 9

123	How long has this anxiety been present? *Record number of months and code as applicable.*	|__|__| months	< 6 Months 0 DK 8 N/A 9	> 6 Months	1
124	Have these changes developed gradually or did they come on suddenly?		Sudden 0 DK 8 N/A 9	Gradual	1

C PARANOID ILLNESS

125	a) Has he/she complained unjustifiably of being persecuted or spied upon?	Yes 1 No 0 DK 8 N/A 9	→	b) Is this a change?	No 0 DK 8 N/A 9	Yes	1

126	a) Has he/she been troubled by voices or visions not experienced by others?	Yes 1	→	b) Is this a deterioration?	Yes	→		
		No 0			No	0		
		DK 8			DK	8		
		N/A 9			N/A	9		

If no paranoid illness, skip to section D and code 127 and 128 as 9

127	How long has he/she experienced this?	|__|__| months	< 6 Months	0	> 6 Months	1
			DK	8		
			N/A	9		
128	Does he/she believe these are real?		No	0	Yes	1
			DK	8		
			N/A	9		

D CLOUDING / DELIRIUM

129	a) Has there been an abrupt change towards mental confusion in recent weeks or months?	Yes 1	→	b) Is this a deterioration?	Yes	→	Slight deterioration	1
							Great deterioration	2
		No 0			No	0		
		DK 8			DK	8		
		N/A 9			N/A	9		

If no confusion, skip to Part 4 on Physical Health and code questions 130 - 135 as 9

130	How long has this confusion been present?	< 6 Months	0	> 6 Months	1
		DK	8		
		N/A	9		
131	Are there periods lasting days or weeks when his/her thinking still seems quite clear?	No	0	Yes	1
		DK	8		
		N/A	9		
132	Are there brief episodes during 24 hours when he/she seems much worse and then times when quite clear?	No	0	Yes	1
		DK	8		
		N/A	9		
133	Does he/she become completely normal when the confusion clears?	No	0	Yes	1
		DK	8		
		N/A	9		
134	Is the confusion worse towards dusk or evening?	No	0	Yes	1
		DK	8		
		N/A	9		
135	Has the present illness tended recently to vary a lot, day to day, week to week, becoming worse and then improving for a while?	No	0	Yes	1
		DK	8		
		N/A	9		

E SUBSTANCE ABUSE

136	Does he/she have a significant history of alcohol or other substance abuse?	No	0	Yes	1
		DK	8		
		N/A	9		

Part 4 Current Physical Health

Instructions to be read to informant:

"The aim of the next set of questions, is to find out about ....'s physical health."

A PHYSICAL DISABILITY

137		Does he/she suffer from poor hearing that interferes with day to day living?	No **0** DK **8** N/A **9**	Yes **1**	
138		If "yes", for how long has this been a problem?	DK **88** N/A **99**	|___|___| months	
139	**a)**	Does he/she suffer from poor eyesight that interferes with day to day living?	No **0** DK **8** N/A **9**	Yes **1**	
140		If "yes", for how long has this been a problem?	DK **88** N/A **99**	|___|___| months	
141	**a)**	Does he/she suffer from other physical problems that interfere with day to day living? *Please specify:*	No **0** DK **8** N/A **9**	Yes **1**	
142		If "yes", for how long has this been a problem?	DK **88** N/A **99**	|___|___| months	

B HYPOTHYROIDISM

143	a)	Does he/she often feel the cold?	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
144	a)	Does he/she have dry skin?	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
145	a)	Does he/she have dry/brittle hair?	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
146	a)	Does he/she seem to have slowed down?	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
147	a)	Has he/she gained weight?	Yes 1 No 0 DK 8 N/A 9	➔	b)	Is this a change?	No 0 DK 8 N/A 9	Yes	1
148		Has he/she ever been told by a doctor that he/she has an under-active thyroid?					No 0 DK 8 N/A 9	Yes	1

C CEREBROVASCULAR PROBLEMS

149	Has he/she ever passed out and then had a brief weakness or difficulty with speech memory or vision?	No 0 DK 8 N/A 9	Yes	1
150	How long ago did this first occur?	DK 8 N/A 9	|__|__| months	
151	Has he/she fallen or been close to falling?	No/rarely 0 DK 8 N/A 9	Once a month or more	1
152	How long ago did this first occur?	DK 8 N/A 9	|__|__| months	

153	Has she ever had a stroke?	No 0 DK 8 N/A 9	Yes 1
154	How long ago did this first occur?	DK 8 N/A 9	I___I___I months

D OTHER PHYSICAL ILLNESS / MEDICATION

155	Does he/she suffer from any other illness that interferes with day to day living? *Describe:*	No 0 DK 8 N/A 9	Yes 1
156	If "yes", for how long has this been a problem?	DK 88 N/A 99	I___I___I months
157	Does he/she currently take any medication? *Specify:*	No 0 DK 8 N/A 9	Yes 1

Appendix T. CAMCOG-DS

SECTION 2 ASSESSMENT OF PATIENT/PARTICIPANT

The assessments in this section should be conducted with the patient/participant.

Part 1 Clinical interview

Each question should be asked as written. Additional questions may sometimes be necessary to clarify inadequate answers.

All items must be coded

Code:	
Participant doesn't know **(DK)**	***8** or **88***
Not asked/not applicable **(N/A)**	***9** or **99***

158	**Date of interview**		

I would like to ask you some questions about how you are feeling.

DEPRESSION

159	**How happy do you feel today:** **happy** **not very happy** **not happy at all?**	Happy **0** No answer **8** N/A **9**	Not very happy	**1**
			Not happy at all	**2**
160	**Do you feel sad or depressed?**	No **0** DK **8** N/A **9**	Occasionally	**1**
			Most of the time	**2**
161	**Are there things that you used to enjoy doing that you don't enjoy any more?** *Record examples:*	No **0** DK **8** N/A **9**	Yes	**1**

162	Have you lost your appetite or become much more hungry than usual? *Specify:*	No DK N/A	0 8 9	Sometimes Most of the time	1 2

CEREBROVASCULAR FUNCTION

163	Do you often have headaches?	No / rarely DK N/A	0 8 9	Yes > 1 per week	1
164	Do you often fall over?	No / rarely DK N/A	0 8 9	Yes > 1 per month	1

SLEEP

165	Do you find it difficult to fall asleep at night?	No DK N/A	0 8 9	Yes	1
166	Do you often wake up in the middle of the night?	No DK N/A	0 8 9	Yes	1
167	Do you often wake up too early in the morning and find it hard to go back to sleep?	No DK N/A	0 8 9	Yes	1

Now I would like to ask you some questions about any difficulties that you may have.

DECLINE IN FUNCTION

168	Are there things that you used to do that you find more difficult now?	No DK N/A	0 8 9	Yes	1
169	Do you find it more difficult to remember things than you used to?	No DK N/A	0 8 9	Yes	1
170	Do you forget where you have left things more than you used to?	No DK N/A	0 8 9	Yes	1
171	Do you forget the names of people you know well?	No DK N/A	0 8 9	Yes	1

Part 2 Cognitive Examination (CAMCOG-DS)

Neuropsychological assessment to be conducted with the patient/participant.

Before commencing, make sure you have the following items:

Stimulus booklet	**Pencil**	**Wristwatch**
Blank sheet of A4 paper	**Envelope**	

It is important that you speak slowly and clearly. If the participant appears not to have heard or understood, repeat the question (unless the item specifically prohibits repetition).

Do not give the correct answer if a wrong answer or no answer is given.

Coding: *Participants who don't know or refuse to give the answer or give a silly answer receive a score of 0 (equivalent to an incorrect answer). A score of 9 is recorded only if a question is not asked. In such cases indicate the reason for the omission of the question.*

'I am going to ask you some questions now to find out about your memory and other skills. Some of them may seem very easy and others may be difficult, but we need to ask everybody the same questions.'

ORIENTATION

172	**What is your name?**	First and surname	**2**
		First name (or surname) only	**1**
		Incorrect	**0**
		Not asked	**9**
173	**What day is it today?**	Correct without prompt	**2**
	If no response ask:	Correct with prompt	**1**
	Is it _______, _______ or _______?	Incorrect	**0**
	(correct day of the week plus two others - correct answer 2nd)	Not asked	**9**
174	**What month is it now?**	Correct without prompt	**2**
	If no response ask:	Correct with prompt	**1**
	Is it _______, _______ or _______?	Incorrect	**0**
	(correct month plus two others - correct answer 1st)	Not asked	**9**
175	**What year is it now?**	Correct without prompt	**2**
	If no response ask:	Correct with prompt	**1**
	Is it _______, _______ or _______?	Incorrect	**0**
	(correct year plus two others – correct answer 3rd)	Not asked	**9**

176	**What is the name of this place?** (*or if tested at home:* **What is this address?**) *If no response ask:* **Is it _______, _______ or ______?** *(correct place plus two alternatives – correct answer 2nd)*	Correct without prompt Correct with prompt Incorrect Not asked	**2** **1** **0** **9**
177	**What is the name of this town (village, city)?** *If no response ask:* **Is it _______, _______ or ______?** *(correct town plus two alternatives – correct answer 1st)*	Correct without prompt Correct with prompt Incorrect Not asked	**2** **1** **0** **9**

LANGUAGE

Comprehension

	Motor Response *If the patient/participant does not complete the full sequence then the whole instruction may be repeated, without change in tone or tempo, to ensure that it has been heard and understood. Prompting and coaching stage by stage are not allowed. For questions 179-181 half marks are given for a partially correct sequence (e.g. left and right confused, only one of the required actions completed or actions completed in the wrong order)* **I am going to ask you to do something, so please listen carefully.**		
178	**Please nod your head.**	Correct Incorrect Not asked	**1** **0** **9**
179	**Please touch your right ear with your left hand.**	Correct Partially correct Incorrect Not asked	**2** **1** **0** **9**
180	**Please look at the ceiling and then look at the floor.**	Correct Partially correct Incorrect Not asked	**2** **1** **0** **9**
181	**Please tap each shoulder twice with two fingers.**	Correct Partially correct Incorrect Not asked	**2** **1** **0** **9**

Expression

Naming

In questions 182 and 183 accurate naming is needed. Descriptions of function or approximate answers are not acceptable. Acceptable answers may depend on local usage. Some items may have more than one correct name (as indicated). Errors include description of function (e.g. 'used for telling time' for watch and approximate answers (e.g. 'weighing machine' for scales or 'light' for lamp).

In the case of approximate answers, you should say 'Can you think of another word for it?'

Tick each item correctly named and enter number correct under total.

182 *Show pencil*
What is this called?
Show wristwatch
What is this called?

Pencil	☐
Watch	☐
Total	**[ ]**
Not asked	**9**

183 **I am going to show you some pictures. Please tell me the name of each one.**
Show pictures for naming in booklet.

Shoe	☐
Computer	☐
Scales	☐
Suitcase	☐
Clock	☐
Lamp	☐
Total	**[ ]**
Not asked	**9**

Fluency

Only if the participant asks for clarification, explain that animals include birds, fish, insects etc. If the participant gets stuck, encourage him/her with 'Can you think of any more?'

Record number correct in one minute(repetitions not to be counted but age and sexual variants should be counted, e.g. calf, cow, bull).

184 **I'd like you to tell me as many different animals as you can. See how many you can think of in one minute.**
List all items:

Number correct	[ ]
Recode for CAMCOG score	
0	**0**
1-4	**1**
5-9	**2**
10-14	**3**
15+	**4**
Not asked	**9**

Definitions

185	**What do you do with a hammer?** *Hit is not enough. Some other detail should be given without prompting.*	Any correct use Incorrect Not asked	**1** **0** **9**
186	**Where do people usually go to by medicine?**	Chemist / pharmacy Incorrect Not asked	**1** **0** **9**
187	**What is a bridge?** *A general (abstract) definition scores 2 and a specific or limited definition scores 1.*	Goes across river etc. Cross the bridge Incorrect Not asked	**2** **1** **0** **9**

Repetition

188	**I am going to say something and I'd like you to repeat it after me: 'People spend money'.**	Correct Partially correct Incorrect Not asked	**2** **1** **0** **9**

MEMORY

New Learning: Incidental Memory

Recall

189	**I showed you some pictures a little while ago. Can you remember what they were?** *Either descriptions or names are acceptable. Tick each item correctly recalled and enter number correct under Total. If participant previously gave an incorrect name in question 183 but recalls it at this stage, score as correct.*	Shoe Computer Scales Suitcase Clock Lamp **Total** Not asked	☐ ☐ ☐ ☐ ☐ ☐ **[ ]** **9**

Recognition

190	**Which one of these pictures did I show you before?**	Shoe Computer Scales Suitcase Clock Lamp **Total** Not asked	☐ ☐ ☐ ☐ ☐ ☐ **[ ]** **9**

Retrieval of Remote Memories

For questions 191 to 194, if the participant does not know the answer then give the clue provided. If the correct answer is given following the clue the participant scores 1.

191	**Who was John Lennon?** *Clue:* **He was in a famous pop group.**	One of the Beatles	**2**
		One of the Beatles (with clue)	**1**
		Incorrect	**0**
		Not asked	**9**
192	**Which Princess died in a car crash in Paris?** *Clue:* **She was married to Prince Charles**	Princess Diana	**2**
		Princess Diana (with clue)	**1**
		Incorrect	**0**
		Not asked	**9**

Retrieval of recent information

193	**Who is the Prime Minister?** *Clue:* **His/her first name is...** (*give first name*)	Correct	**2**
		Correct with clue	**1**
		Incorrect	**0**
		Not asked	**9**
194	**What is the name of the present king or queen?** *Clue:* **It begins with...** *(give first letter)*	Correct	**2**
		Correct with clue	**1**
		Incorrect	**0**
		Not asked	**9**

ATTENTION / CONCENTRATION

195	**I would like you to count to twenty for me.** *Record highest number reached before an error is made. Recode for CAMCOG score.*	Highest number reached before error	**[ ]**
		Recode (number reached before error)	
		20	**4**
		15-19	**3**
		10-14	**2**
		5-9	**1**
		<5	**0**
		Not asked	**9**

196	*Hold up 1^{st}, 2^{nd} and 3^{rd} fingers:* **Look at my fingers. See, I'm holding up three fingers.** *Then hold up 1^{st} finger:* **Now I'm holding up 1 finger.** *Then hold up 1^{st} and 4^{th}:* **Now you count my fingers. Yes, two fingers.** *Then hold up 1^{st} finger only. If participant doesn't spontaneously count fingers say:* **I want you to count my fingers, keep counting, don't stop.**			
	Tick each presentation that is counted spontaneously. Score as described.	*1^{st} and 4^{th}*	2	☐
		1^{st}	1	☐
		1^{st} 2^{nd} and 3^{rd}	3	☐
		4^{th}	1	☐
		all 4 fingers	4	☐
			All correct (no prompt)	**2**
			1 prompt	**1**
			More than 1 prompt	**0**
			Not asked	**9**
197	**I'm going to say some numbers and I'd like you to repeat them after me…**		2	☐
			5	☐
			8-7	☐
	Read each number string once. Tick each series correctly repeated. Discontinue after failure on both series of a given length. Score as described.		4-1	☐
			5-8-2	☐
			6-9-4	☐
			6-4-3-9	☐
			7-2-8-6	☐
			4-2-7-3-1	☐
			7-5-8-3-6	☐
			4 or 5 digit series correct	**3**
			2 or 3 digit series correct	**2**
			1 digit repeated	**1**
			0 correct	**0**
			Not asked	**9**

LANGUAGE

Comprehension

	Reading *Show reading comprehension in booklet.* *It is not necessary for the participant to read aloud. If participant reads instruction but fails to carry out action, say 'now do what it says'*		
198	**I would like you to read this and do what it says.**		
	'Close your eyes'	Correct Incorrect Not asked	1 0 9
199	**'Give me your hand'**	Correct Incorrect Not asked	1 0 9

PRAXIS

Copying and drawing

	The participant should draw on the sheet of paper provided (p. 49).		
200	**Copy this shape (circle)** *A closed circular shape (circle, oval or ellipse) is required*	Correct Incorrect Not asked	1 0 9
201	**Copy this shape (square)** *A closed four sided shape (square or rectangle) is required*	Correct Incorrect Not asked	1 0 9
202	**Copy this picture (3D house)** *Tick each component successfully completed and enter number under Total*	Outline of house Windows, doors and chimney in correct positions 3D representation	□ □ □
		Total Not asked	[ ] 9
203	**Draw a large clock and put all the numbers on it.** *When participant has done this say* **'Now set the hands to 10 past 11'.** *Tick each component successfully completed and enter number under Total*	Circle or square All numbers in correct position Correct time	□ □ □
		Total Not asked	[ ] 9

MEMORY

Registration

204	*Show picture of John Brown in booklet* **This is John Brown. Try to remember his name.** *Short pause.* **What is his name?**	Correct One name only Incorrect Not asked	**2** **1** **0** **9**
	If incorrect or partially correct say **'his name is John Brown'**		
205	**I'm going to tell you where he lives. See if you can remember. He lives at:** **42 West Street, Bedford.** *Short pause* **Where does he live?**	Correct Partially Correct Incorrect Not asked	**2** **1** **0** **9**
	If incorrect or partially correct say **'he lives at 42 West Street, Bedford'**		
	Please try to remember his name and address as I will be asking you about them later on.		

PRAXIS

Ideomotor

	For questions 206 to 208, a correct mime is needed. If the participant uses fingers to represent scissors or brush, say e.g. 'Pretend you are holing a toothbrush'. Score 1 if brushing movement is made but not as though holding a toothbrush.		
206	**Show me how you wave goodbye.**	Correct Incorrect Not asked	**1** **0** **9**
207	**Show me how you would cut with scissors.**	Correct Partially Correct Incorrect Not asked	**2** **1** **0** **9**
208	**Show me how you would brush your teeth with a toothbrush.**	Correct Partially Correct Incorrect Not asked	**2** **1** **0** **9**

Ideational

	Read the following statement and then hand a sheet of paper to the participant. Make a point of handing to the participant's midline. No repetition of this question is allowed. Speak slowly and clearly, having first made sure you have the participant's full attention.		
209	**I am going to give you a piece of paper. When I do, take the paper in your right hand. Fold the paper in half with both hands, and put the paper down on your lap.**	Right hand Folds On lap	□ □ □
	Do not repeat instructions or coach. *Score a move as correct only if it takes place in the correct sequence. Tick each correct move and enter number correct under total.*	**Total** Not asked	[ ] 9
210	*Hand envelope to participant*		
	Put the paper in the envelope and seal the envelope.	Correct Incorrect Not asked	1 0 9

MEMORY

Intentional Learning

	Recall		
211	*Show picture of John Brown in booklet* **What was this man's name?**	Full name correct Partially correct Incorrect Not asked	2 1 0 9
212	**What was his address?** *Tick each item recalled correctly and enter number correct under Total*	42 West Street Bedford	□ □ □
		Total Not asked	[ ] 9

ABSTRACT THINKING

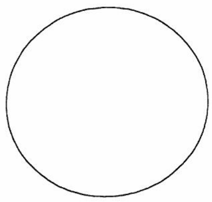
These questions investigate the capacity to work out general relationships between objects. Fully correct answers score 2. Partially correct answers score 1. Examples are given beside each score if the participant says 'They are not alike', say 'They are alike in some way. Can you tell me in which way are they alike?'

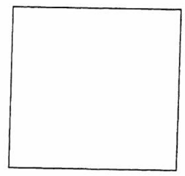
I am going to name two things and I would like you to tell me in what way they are alike. For example a dog and a monkey are alike because they are both animals.

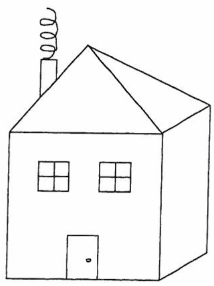
213	**In what way are an apple and a banana alike?**	Fruit	2
		Food, grow, have peel	1
	Record answer	Round, have calories	0
	For this question only, if incorrect say **'they are also alike because they are both kinds of fruit'.**	Not asked	9
214	**In what way are a shirt and a dress alike?**	Clothing	2
	Record answer	To wear, made of cloth, keep warm	1
		Have buttons	0
		Not asked	9
215	**In what way are a table and a chair alike?**	Furniture	2
	Record answer	Household objects, used for meals	1
		Wooden, 4 legs	0
		Not asked	9

VISUAL PERCEPTION

216	*Show 'Recognition of famous people' in booklet*		
	Who is this?	Queen	☐
		Pope, Archbishop, Bishop	☐
	Score as correct if picture is recognised.		
	Correct name is not required, but record any answer that does not correspond exactly to the examples given.	**Total**	[ ]
		Not asked	9
217	*Show 'Recognition of objects' in booklet*		
	These pictures are taken from unusual angles.	Spectacles	☐
	Can you tell me what they are?	Shoe	☐
		Purse/suitcase	☐
	Criterion is whether object is recognised but not that it is named correctly, therefore descriptions of function are acceptable. Tick each item answered correctly and enter number correct under Total	Cup and saucer	☐
		Telephone	☐
		Pipe	☐
		Total	[ ]
		Not asked	9







Clock

CAMCOG-DS Scoring Summary Chart

Participant's Name ______________________________ Assessment Date ___/___/_____

ORIENTATION

		Max
172 Name		(2)
173 Day		(2)
174 Month		(2)
175 Year		(2)
176 Address		(2)
177 Town		(2)
Orientation Total		**(12)**

LANGUAGE

Comprehension		
178 Nod		(1)
179 Ear		(2)
180 Ceiling		(2)
181 Shoulder		(2)
198 Eyes		(1)
199 Hand		(1)
Total		**(9)**

Expression		
182 Objects		(2)
183 Pictures		(6)
184 Fluency		(4)
185 Hammer		(1)
186 Chemist		(1)
187 Bridge		(2)
188 Repetition		(2)
Total		**(18)**
Language Total		**(27)**

MEMORY

New Learning		Max
189 Recall pictures		(6)
190 Recognition		(6)
204 Register name		(2)
205 Register address		(2)
211 Recall name		(2)
212 Recall address		(3)
Total		**(21)**

Remote		
191 Lennon		(2)
192 Diana		(2)
Total		**(4)**

Recent		
193 Prime Minister		(2)
194 Monarch		(2)
Total		**(4)**
Memory Total		**(29)**

ATTENTION

195 Twenty		(4)
196 Fingers		(2)
197 Digit-span		(3)
Attention Total		**(9)**

PRAXIS

Drawing/copying		Max
200 Circle		(1)
201 Square		(1)
202 House		(3)
203 Clock		(3)
Total		**(8)**

Actions to command		
206 Wave		(1)
207 Scissors		(2)
208 Toothbrush		(2)
209 Paper		(3)
210 Envelope		(2)
Total		**(10)**
Praxis Total		**(18)**

ABSTRACT THINKING

213 Fruit		(2)
214 Clothing		(2)
215 Furniture		(2)
Abstr. Thinking Total		**(6)**

PERCEPTION

216 People		(2)
217 Unusual views		(6)
Total		**(8)**

TOTAL SCORE		**(109)**

Part 3 Interviewer Observations

To be recorded at the end of the patient/participant assessment.
Code 'Yes' only if characteristic is markedly present.

218	**Self-neglect**	No	0	Yes	1
219	**Uncooperative behaviour**	No	0	Yes	1
220	**Suspiciousness**	No	0	Yes	1
221	**Hostility or irritability: e.g. angry response**	No	0	Yes	1
222	**Silly, incongruent or bizarre behaviour**	No	0	Yes	1
223	**Slowness and underactivity: e.g. sits abnormally still, delay in response to questions.**	No	0	Yes	1
224	**Restlessness: e.g. fidgeting, pacing, unnecessary movements.**	No	0	Yes	1
225	**Anxiety and fear: appears frightened, worried or somatically tense out of proportion to the situation.**	No	0	Yes	1
226	**Depressed mood: looks sad, mournful, tearful, voice low or gloomy**	No	0	Yes	1
227	**Lability of mood: rapidly changes from sad to happy, friendly to irritable.**	No	0	Yes	1
228	**Flat affect: lack of spontaneous emotion or emotional response to interviewer, monotonous voice, lack of gestures**	No	0	Yes	1
229	**Hallucinating: behaves as though hears voices or sees visions, or admits to doing so.**	No	0	Yes	1
230	**Speech very rapid and difficult to follow.**	No	0	Yes	1
231	**Speech very slow with pauses between words.**	No	0	Yes	1
232	**Speech restricted in quantity: e.g. answers questions but no spontaneous expressions.**	No	0	Yes	1

233	Speech rambling or incoherent, irrelevant answers to questions.	No	0	Yes	1
234	Speech slurred.	No	0	Yes	1
235	Perseveration.	No	0	Yes	1
236	Clouding of consciousness.	No	0	Yes	1
237	Speaks to self	No	0	Yes	1
238	Impaired ability to focus, sustain or shift attention.	No	0	Yes	1
239	Hypochondriacal preoccupations with somatic discomfort.	No	0	Yes	1

Tower of London Task

Procedure adapted from Kirkorian, Bartok & Gay, 1994, J Clin Exptl Neuropsychology, 16, 6, 840-850.

Sit opposit the participant and place the two boards with the longest peg on the participant's left and the numbers 1, 2, 3 pointing towards you; one in front of them, with the beads in the start position, and one in front of you, with the beads in the practice trial position (Practice 1).

Say "**I want you to move the beads on your pegs to make them the same as the beads on my pegs.**"When they have done it say, "**that's good. That's the idea. Each time we'll start with your beads like this** (arrange the beads into the start position). **I'll change mine and you have to make yours the same as mine. I also want you to do it in a certain number of moves. A move means taking a bead from a peg and putting it on another peg. There are two rules. You can only pick up one bead at a time so you can't do this** (pick up two beads in one hand) **or this** (pick up on bead in each hand). **You can't put the beads down on the table. If you get stuck we can go back to the beginning. Shall we have a practice?**"Arrange your board to the first practice problem again. Say, "**Now, try and make yours look like this in two moves.**"

Provide feedback if the participant tries to make an illegal move and about the number of moves allowed. Say, "**Remember the rule. You can't……. . Let's start again. Have another go. Remember that you have to do it in (X) moves.**"
Provide one more practice trial with feedback as above.
After practice, go through the problems in the order presented on the sheet and continue to provide feedback if the participant tries to make an illegal move and about the number of moves allowed for the problem. Say, "**Remember the rule. You can't……. . Let's start again. Have another go. Try again. Remember that you have to do it in (X) moves.**"

Discontinue after three consecutive failed problems (i.e. 9 consecutive failed trials).

Scoring

The pegs are labelled 1, 2, 3 (small to large) and the beads are called R, G, B. Write down the moves the participant makes on the score sheet. The problem is solved if the end position is achieved in the required number of legal moves.

A trial ends if the participant realises that the trial will not succeed or if an illegal move is made. The beads are then reset to the start position for the next trial. Do not provide feedback after each incorrect move, wait until the end of the trial.
A participant is allowed to modify a move if they are still holding a bead.

Three trials will are allowed for each problem. Three points are scored if the problem is solved on the first trial, two if on the second trial, and on point if on the third.

Tower of London Task – Record Sheet

Name.. Subj. number....................... Assessor.........................

Start position R
B G
1 2 3

Practice 1 R-1/B-3 B
R G
1 2 3

Practice 2 R-2/G-1 R
G B
1 2 3

Trial	Target	# moves	Correct response	Subject response	Score
1	B R G	2	B-1/R-2		3 2 1
2	G B R	3	B-1/R-2/G-2		3 2 1
3	G R B	4	B-1/R-2/G-2/B-3		3 2 1
4	G R B	5	B-1/R-2/G-2/B-3/ G-3		3 2 1
				Total score	

Scrambled Boxes

Equipment: Small boxes with shapes on. Three coins.

Stationary condition

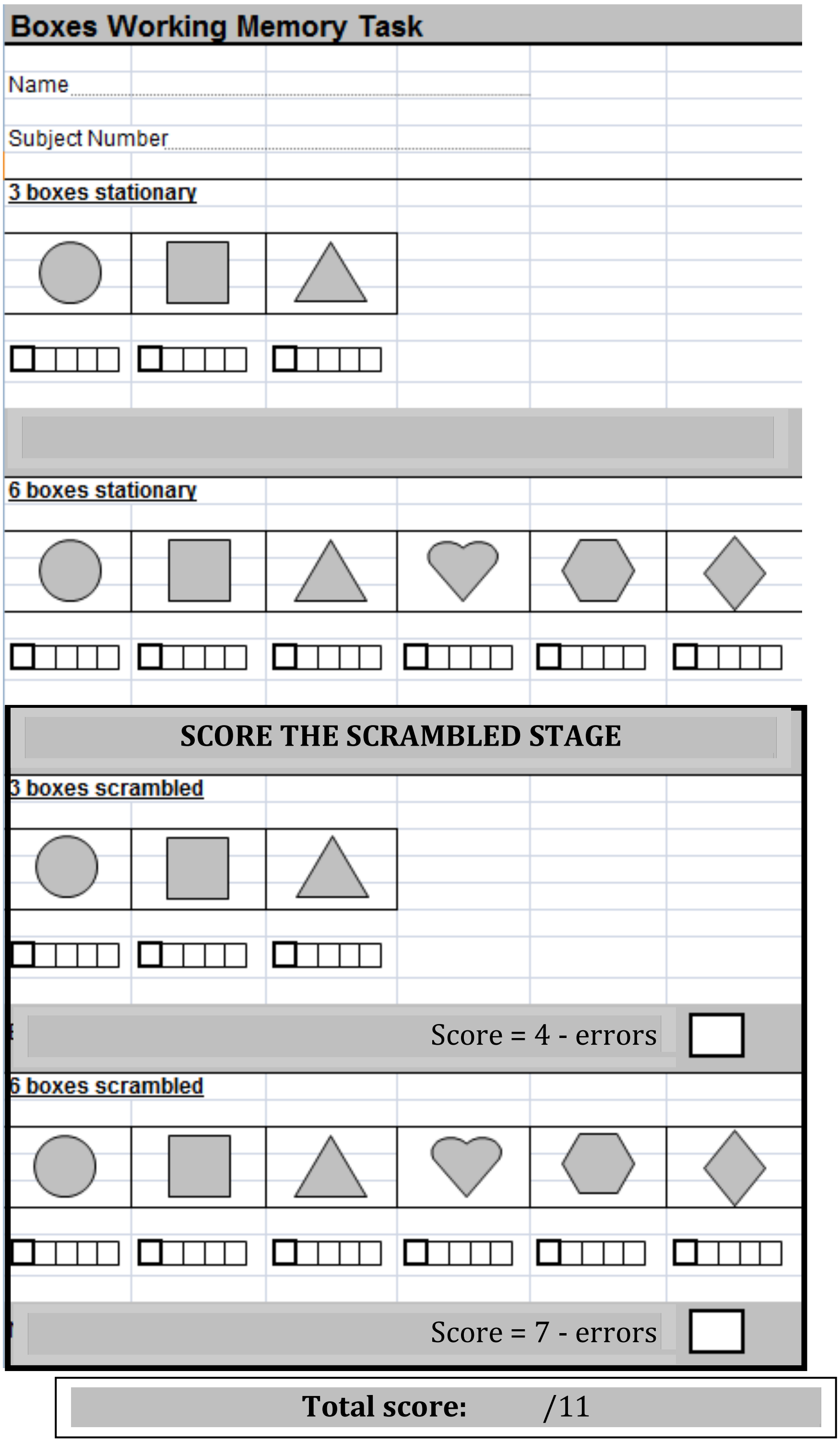
Say to the participant, "I am going to put a coin under each of these boxes". Th*en hide the coins. After a short delay, say,* **"I would like you to choose one of the boxes and look under it to see if you can find a coin."**

After the participant has found a coin, remove it and say, **"Now lets put that box back and try to find another coin."** After replacing the empty box in its original position, say, **"This time I would like you to choose a box you haven't looked in before. Try not to choose an empty one."**
If participant successfully chooses a full box then say **"Well done! Now try again and see if you can find another coin. Try to choose a box you haven't looked under before"**
If participant chooses the empty box then say **"Oh dear it's empty. Never mind, let's have another go. Try to choose a box you haven't looked in before"**
Repeat as above until participant has found all the coins or has made FOUR of errors.
If participant successfully finds all coins then say **"Well done, you've found all the coins now. Let's try the same thing again but this time, to make it a bit more difficult, I'm going to move the boxes around."**

Scrambled condition

Say, **"I am going to put a coin under each of the boxes again".** Then *hide the coins .*
After a short delay, say, **"Now I'm going to mix them up. I would like you to choose one of the boxes and look under it to see if you can find a coin.** *While giving this instruction mix up the location of the boxes while the participant watches.*
When the participant finds a coin, say "Now let's put that box back and try to find another coin."
Replace empty box and after a short delay, say to them, **"I'm going to mix the boxes up again and I would like you to choose a box you haven't looked in before. Try not to choose an empty one."** *While giving this instruction mix up the location of the boxes again while the participant watches.*
If participant successfully chooses a full box then say, **"Well done! Now try again and see if you can find another coin. Try to choose a box you haven't looked under before."** *Again, while giving this instruction mix up the location of the boxes while the participant watches.*
If participant chooses the empty box then say **"Oh dear it's empty. Never mind, let's have another go. Try to choose a box you haven't looked in before"** *Again, while giving this instruction mix up the location of the boxes while the participant watches.*

Continue until participant has found all the coins or made FOUR of errors.
If the participant completes both the stationary and scrambled stages with three boxes, then repeat the process with SIX boxes. In this case, testing continues until all the coins have been retrieved or until SEVEN errors have been made.



Boxes Working Memory Task

Name

Subject Number

3 boxes stationary

6 boxes stationary

SCORE THE SCRAMBLED STAGE

3 boxes scrambled

Score = 4 - errors

6 boxes scrambled

Score = 7 - errors

Total score: /11

Appendix W. Script: print cluster

```
function printcluster(conname,modality,varargin)

loadpaths

param = finputcheck(varargin, { ...
    'dir', 'string', {'pos','neg','both'}, 'both'; ...
    'alpha', 'real', [], 0.05; ...
    'statwin', 'real', [], [-200 700]; ...
    });

%sampling period of data
samptime = 4;

if isnumeric(modality)
    %source
    modality_or_val = sprintf('%d',modality);
elseif ischar(modality)
    %sensor
    modality_or_val = modality;
end

%% load contrast and identify clusters
load(sprintf('%s%s_stat_%s.mat',filepath,conname,modality_or_val),'st
at');

if ischar(modality) && ~isempty(stat.clusters)
    timeline = stat.statwin(1):samptime:stat.statwin(2);
    statwinidx =
intersect(find(timeline>=stat.statwin(1)),find(timeline<=stat.statwin
(2)));

    %select clusters within specified time window
    selectclusters = timeline(statwinidx(1) +
cell2mat({stat.clusters.tstart}) - 1) >= param.statwin(1) & ...
        timeline(statwinidx(1) + cell2mat({stat.clusters.tstop}) - 1)
<= param.statwin(2);
    stat.clusters = stat.clusters(selectclusters);

    %select clusters in specified direction (positive/negative)
    selectclusters = false(1,length(stat.clusters));
    for c = 1:length(stat.clusters)
        plottimeidx = statwinidx(1) + stat.clusters(c).tmax -1;
        clustpeak = diffcond(:,:,plottimeidx);
        clustsum = sum(clustpeak(stat.mask(:,:,stat.clusters(c).tmax)
== stat.clusters(c).clusternum));
        if (strcmp(param.dir,'both') || strcmp(param.dir,'pos')) &&
clustsum > 0
            selectclusters(c) = true;
        elseif (strcmp(param.dir,'both') || strcmp(param.dir,'neg'))
&& clustsum < 0
            selectclusters(c) = true;
        end
    end
    stat.clusters = stat.clusters(selectclusters);



end
```

```
if ~isempty(stat.clusters)
    [~,maxclustidx] = max(cell2mat({stat.clusters.clustersize}));
else
    warning('No clusters found!');
    maxclustidx = [];
end

if ~isempty(maxclustidx)
    if stat.clusters(maxclustidx).clusterpval < param.alpha
        if stat.clusters(maxclustidx).clusterpval >= 0.00001
            fprintf('Cluster %d: %d-%dms, peak %dms, p = %.5f.\n',...
                stat.clusters(maxclustidx).clusternum,...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tstart - 1),...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tstop - 1),...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tmax - 1),...
                stat.clusters(maxclustidx).clusterpval);
        else
            fprintf('Cluster %d: %d-%dms, peak %dms, p = %.1e.\n',...
                stat.clusters(maxclustidx).clusternum,...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tstart - 1),...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tstop - 1),...
                timeline(statwinidx(1) +
stat.clusters(maxclustidx).tmax - 1),...
                stat.clusters(maxclustidx).clusterpval);
        end
    else
        warning('No significant clusters found!');
    end
end
```

Appendix X. Script: extract global field power values

```
function outdata = runstats(listname,condlist,covariateidx,varargin)

loadpaths
loadsubj

subjlist = eval(listname);

param = finputcheck(varargin, { ...
    'channame', 'cell', ''   ; ...
    'measure','string',{'mean','latency'},'max'; ...
    'timewin', 'real', [], []; ...
    });

if ischar(param)
    error(param);
end

if ischar(listname)
    listname = repmat({listname},size(condlist));
end

filesuffix = '_cond';

for c = 1:length(condlist)
        filecondname{c} = sprintf('%s',condlist{c});
end

for s = 1:size(subjlist,1);
    subjname = lower(subjlist{s,1});
    file2load = sprintf('%s%s%s.mat',filepath,subjname,filesuffix);
    fprintf('Loading %s.\n',file2load);
    D = spm_eeg_load(file2load);

    if s == 1
        timevals = D.time*1000;
        timewinidx = [find(min(abs(timevals-param.timewin(1))) ==
abs(timevals-param.timewin(1))) ...
            find(min(abs(timevals-param.timewin(2))) == abs(timevals-
param.timewin(2)))];
        for c = 1:length(param.channame)
            chanidx(c) =
find(strcmp(param.channame{c},D.chanlabels));
        end
            end

gfpdata = zeros(size(subjlist,1),length(timevals),length(condlist));

    for c = 1:length(condlist)
        filecondidx = find(strcmp(filecondname{c},D.conditions));
        [~,gfpdata(s,:,c)] =
evalc('eeg_gfp(D(setdiff(1:D.nchannels,D.badchannels),:,filecondidx)'
')''');
    end


gfpdata = gfpdata(:,:,1) - gfpdata(:,:,2);
elseif strcmp(param.measure,'mean')
    statdata = max(gfpdata(:,timewinidx(1):timewinidx(2)),[],2);
```

```
elseif strcmp(param.measure,'latency')
    [~,statdata] = max(gfpdata(:,timewinidx(1):timewinidx(2)),[],2);
    statdata = timevals(statdata+timewinidx(1)-1)';
end
      end
```

Appendix Y. Sensitivity analysis

The table below details the number of outliers for each GFP maxima and latency, by group.

GFP maxima time-windows (ms)	Associated ERP	Number of outliers for the GFP Maxima, by group		Number of outliers for the latencies, by group	
		DS	C	DS	C
100-200	MMN	0	2	0	0
200-400	P300 (a,b)	1	3	4	0
400-650	P3b	1	N/A	0	N/A

The following sections detail the results of the analyses when the outliers have been removed, to find no significant changes.

Chapter 4: age

Spearman's Rank-Order correlations (one-tailed) between age and the GFP maxima and latencies (MMN, P3a, P3b), without the outliers, revealed no significant results, which is the same as the analyses in which they are included. The test statistics are as follows. For the controls, age correlated with neither GFP maxima for MMN (r = .233, p = .083) or P3b GFP maxima (r = -.086, p = .310). For the adults with DS, age correlated with neither GFP maxima for P3a (r = -.124, p = .239) or P3b (r = -.094, p = .295). Age also did not correlate with P3a latency (r = .172, p = .173), for adults with DS.

Chapter 5: executive function

Spearman's Rank-Order correlations (two-tailed) between the summary cognitive measures (CAMCOG, EFDS, KBIT II – raw, standardized) and the GFP maxima and latencies (P3a, P3b), without the outliers revealed no significant results, which is the same as the analyses in which they are included. For the adults with DS, P3a GFP maxima correlated with none of the following summary measures: CAMCOG (r = -.214, p = .28); EFDS (r = .037, p = .813); KBIT II standardized (r = -.272, p = .114); KBIT II raw scores (r = -.266, p = .122). P3a latency also did not correlated with any of the summary measures: CAMCOG (*r* = .147, *p* = .423); EFDS (*r* = .041, *p* = .825); KBIT II standardized (*r* = -.055, *p* = .767); KBIT II raw scores (*r* = -.083, *p* = .650). P3b GFP maxima also did not correlated with any of the summary measures: CAMCOG (*r* = -.052, *p* = .766); EFDS (*r* = -.024, *p* = .889); KBIT II standardized (*r* = -.008, *p* = .963); KBIT II raw scores (*r* = .020, *p* = .909).

Chapter 6: cognitive decline

Spearman's Rank-Order correlations (two-tailed) between the global cortical ROI PIB binding values and the GFP maxima and latencies (P3a, P3b), without the outliers, revealed no significant results, which is the same as the analyses in which they are included. For the adults with DS, cortical PIB binding correlated with neither GFP maxima for P3a (*r* = .264, *p* = .433) or P3b (*r* = .382, *p* = .247). Cortical PIB bindings also did not correlate with P3a latency (*r* = -.119, *p* = .761), for adults with DS.

Spearman's Rank-Order correlations (two-tailed) between the total CAMCOG difference (T2-T1) scores and the GFP maxima and latencies (P3a, P3b), without the outliers, revealed no significant results, which is the same as the analyses in which they are included. For the adults with DS, CAMCOG change correlated with neither GFP maxima for P3a (*r* = -.020, *p* = .910) or P3b (*r* = -.015, *p* = .933). CAMCOG change also did not correlate with P3a latency (*r* = -.030, *p* = .873), for adults with DS.

Appendix Z. Correlations between the raw KBIT-II composite scores and the ERPs

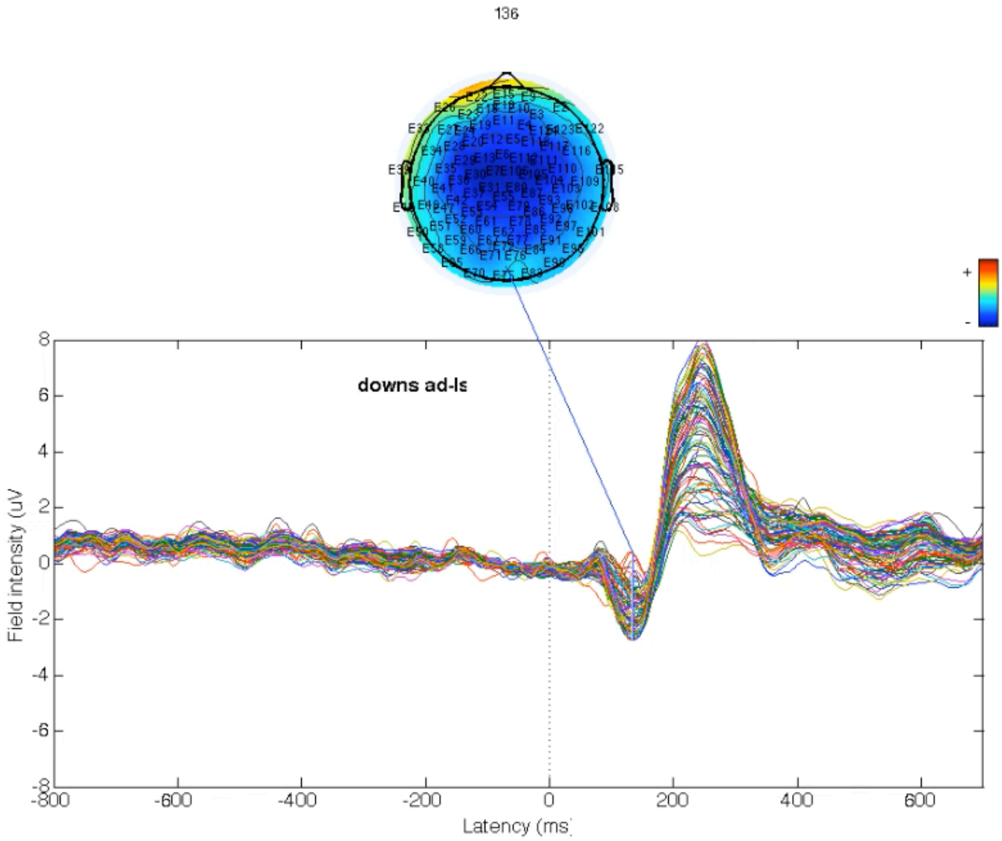
The range of raw KBIT-II composite scores for the adults with DS was 80 to 179, M = 115.8. SD = 22.3. The correlations between the raw scores and the ERPs were not significant. The test statistics can be found in the table below.

Raw KBIT-II scores	GFP maxima time-windows (ms)	Associated ERP	Corelation with GFP Maxima		Correlation with GFP maxima latencies	
			r	*p*	*r*	*p*
Composite	100-200	MMN	-.323	.055	.114	.510
	200-400	P3a	-.304	.071	-.053	.759
	400-650	P3b	-.008	.964	.136	.428

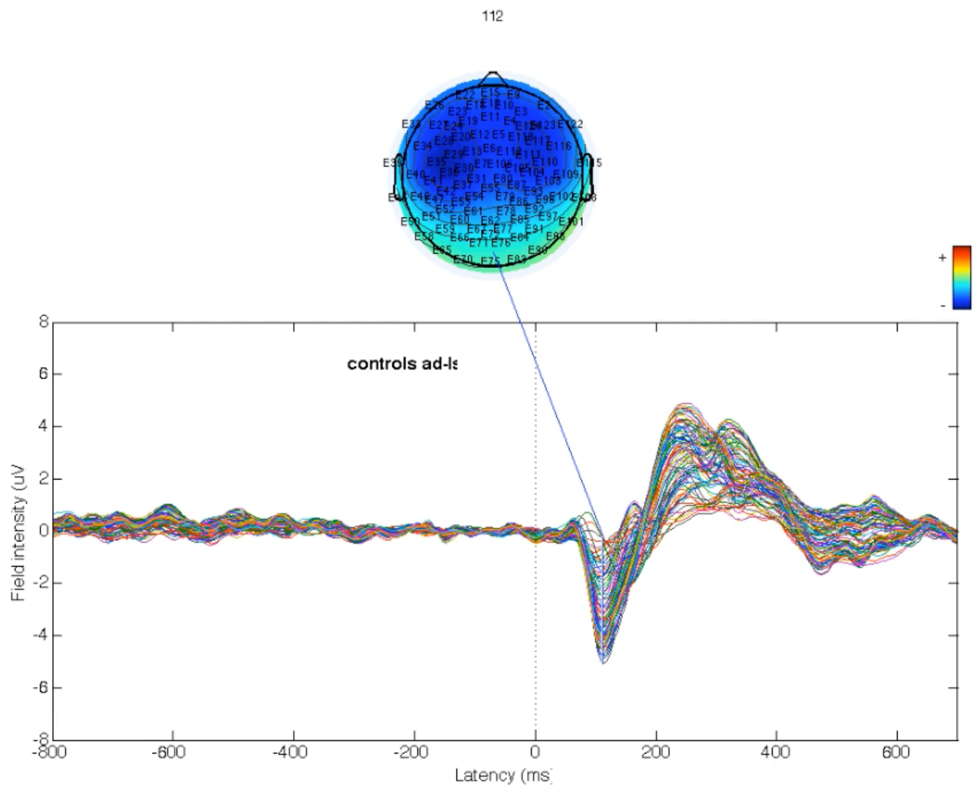
Spearman's Rank-Order correlations (two-tailed) between the raw KBIT-II composite scores and the GFP maxima and latencies (MMN, P3a, P3b).

Appendix AA. Waveform visualisations

The figures below depict the distribution of the EEG waveforms over the time-course. Each line maps an individual's response to stimuli, with 0 indicating the onset of a deviant stimulus. The scalp maps are focused on the negative, MMN response (100-200ms). However, the whole time-course, which includes the P300 responses (200-400ms), is mapped.



Mapping the EEG waveforms for participants' with DS responses to deviant stimuli.



Mapping the EEG waveforms for TD control participants’ responses to deviant stimuli.